

RESEARCH ARTICLE

Morphological determinants of glycosylation efficiency in Golgi cisternae

Christopher K. Revell^{1,2*}, Martin Lowe², Nicola L. Stevenson³, Oliver E. Jensen¹

1 Department of Mathematics, University of Manchester, Manchester, United Kingdom, **2** School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom, **3** Cell Biology Laboratories, School of Biochemistry, Faculty of Life Sciences, University of Bristol, Bristol, United Kingdom

* christopher.revell@manchester.ac.uk



OPEN ACCESS

Citation: Revell CK, Lowe M, Stevenson NL, Jensen OE (2026) Morphological determinants of glycosylation efficiency in Golgi cisternae. *PLoS Comput Biol* 22(3): e1013993. <https://doi.org/10.1371/journal.pcbi.1013993>

Editor: Jian Liu, JHU, UNITED STATES OF AMERICA

Received: November 14, 2025

Accepted: February 6, 2026

Published: March 6, 2026

Copyright: © 2026 Revell et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data availability statement: All code used to generate and analyse the results in this manuscript can be found on Zenodo <https://doi.org/10.5281/zenodo.18232405>.

Funding: CKR, NLS, OEJ, and ML were supported by the Biotechnology and Biological Sciences Research Council award number BB/T001984/1 (<https://www.ukri.org/councils/>)

Abstract

The Golgi apparatus has an intricate spatial structure characterized by flattened membrane-bound compartments, known as cisternae. Cisternae house integral membrane enzymes that catalyse glycosylation, the addition of polymeric sugars to protein cargo, which is important for the trafficking and function of the products. The unusual and specific shape of Golgi cisternae is highly conserved across eukaryotic cells, suggesting significant influence in the correct functioning of the Golgi. Motivated by experimental evidence that disruption to Golgi morphology can lead to observable changes in secreted cargo mass distribution, we develop and analyse a mathematical model of polymerisation in a cisterna that combines chemical kinetics, spatial diffusion and adsorption and desorption between lumen and membrane. Exploiting the slender geometry, we derive a non-local non-linear advection-diffusion equation that predicts secreted cargo mass distribution as a function of cisternal shape. The model predicts a maximum cisternal thickness for which successful glycosylation is possible, demonstrates the existence of an optimal thickness for most efficient glycosylation, and suggests how kinetic and geometric factors may combine to promote or disrupt polymer production.

Author summary

The Golgi apparatus is a universal feature of eukaryotic cells, playing a critical role in post-translational modification of secreted proteins. Its importance is demonstrated by the variety of disorders caused by errors in its function. A major post-translational modification is glycosylation: the addition of sugar chains to protein cargo. The Golgi has a distinctive structure, being comprised of stacks of thin, hollow, flattened, cisternae. We develop a mathematical model of glycosylation, combining enzyme-mediated membrane-bound reactions with intra-cisternal diffusion, to quantify the effect of cisternal morphology on processing rate. The

[bbsrc/](#)) and NLS by Medical Research Council award number UKRI1419 (<https://www.ukri.org/councils/mrc/>). The funders played no direct role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have no competing interests to declare.

model identifies optimal and maximal cisternal thicknesses for glycosylation to proceed, in terms of biochemical parameters. The model offers a quantitative connection between the Golgi's cisternal morphology and its function.

Introduction

The Golgi apparatus is a critical organelle and a defining feature of eukaryotic cells [1–4]. It is typically comprised of between four and seven membranous compartments called cisternae, each of which have a distinctive flattened geometry reminiscent of a pita bread [5–7]. Each cisterna has a cylindrical diameter of roughly 1 μm and a depth of roughly 20–60 nm [8], indicating a spatial asymmetry of about 2 orders of magnitude that generates a high surface-area-to-volume ratio. This ratio is often further enhanced by the presence of fenestrations. The cisternae within the Golgi apparatus are categorised into three “maturation” states (*cis*, *medial*, and *trans*), each characterised by their enzymatic and biochemical composition. The *cis* cisternae are the entry point for cargo; *medial* cisternae are the intermediate maturation state; and the *trans* cisternae are the final compartments preceding cargo sorting and Golgi exit in the *trans*-Golgi network. Among competing theories of the cisternal maturation mechanism, one posits that stable Golgi cisternae exist with a given maturation state, and cargo is exchanged between them via transport vesicles [9], whereas another proposes that Golgi cisternae mature dynamically from one state to the next, driven by the recycling of Golgi resident proteins, whilst retaining their cargo and moving steadily through the stack, as though on a conveyor belt [10,11]. Consensus seems to mostly favour the latter, but this does not affect our primary aim, which is to understand how cisternal shape influences Golgi function.

In humans, approximately 30% of all proteins pass through the Golgi. Any errors in the modification and trafficking of these products can lead to a wide variety of disorders [12–15], highlighting the importance of the Golgi apparatus for cellular function. Genes encoding proteins destined for the secretory pathway are transcribed in the nucleus to produce mRNA molecules bearing signal sequences that direct them to specific domains on the endoplasmic reticulum (ER). Here they form a template for the synthesis of protein chains and are co-translationally imported into the ER. After folding and post-translational modification, for example by disulphide bond formation or addition of N-linked glycans, proteins exit the ER and are transported to the Golgi apparatus where they are further modified and sorted for transport to their next cellular destination.

In most organisms, Golgi cisternae are stacked in close apposition with a *cis*–*trans* polarity established by directional transport. This stacking, whilst highly conserved, is not essential to survival as multiple independent events of unstacking can be observed in evolution, such as in the yeast *Saccharomyces cerevisiae* [16]. In many higher organisms, cisternae are also laterally connected to form a Golgi ‘ribbon’ architecture, a feature that evolved as a new functionalisation in the last common ancestor of cnidarians and bilaterians [17]. In contrast to stacking and lateral tethering, the

overall geometry of a flattened cisterna has been universally conserved since the last eukaryotic common ancestor [3,17]. It is therefore an ancient feature, suggesting that this morphology has a fundamental role in Golgi function. Despite this, very little is known regarding its functional relevance. This is due, in part, to experimental limitations, since the methods currently available to perturb cisternal flattening inevitably have pleiotropic impacts on Golgi biology. Genetic perturbation of the Golgi organising proteins GOLPH3 [18] or GMAP210 [19–23], or of the Golgi anion exchanger AE2 [24], will induce cisternal dilation, as will drug-induced disruption to actin polymerisation [25]. However, in each case other aspects of Golgi organisation, trafficking and chemistry are affected. Alternative approaches are therefore required to isolate this feature.

One of the major post-translational modifications orchestrated by the Golgi is the sequential addition of carbohydrate residues (monosaccharides, that we henceforth refer to as substrate) to cargo proteins to form glycan chains [26]. This process, called glycosylation [27], is mediated by enzymes anchored into the membrane of the Golgi cisternae via trans-membrane protein domains, with the catalytic domain protruding into the lumen [28]. Unlike peptides, the synthesis of glycan structures is not templated and must be regulated by controlling conditions within the secretory pathway. This is achieved by controlling the cohort of enzymes expressed and their relative abundance, the density of sugar transporters and availability of monosaccharide substrates, the distribution of enzymes across the cisternal stack, the transport dynamics of cargo, and the spatial relationships between enzymes and substrates. As a result of these competing factors, the glycan profiles produced by any given cell population are generally heterogeneous. Existing studies are slowly beginning to unpick the relative contribution of many of these control points to glycosylation outcomes. However, the role of Golgi morphology has remained particularly enigmatic.

In this study we use mathematical and computational modelling to assess the relationship between cisternal shape and efficient glycosylation. The membrane-bound nature of the glycosylation reaction suggests that the Golgi apparatus would perform most efficiently with a high surface-area-to-volume ratio, an intrinsic feature of the flattened morphology adopted by the cisternae. Other organelles with membrane-based functions, such as mitochondria, also have a high surface-area-to-volume ratio, however this is achieved through alternative adaptations such as the folding of membranes into cristae.

Previous theoretical studies have examined a number of organisational features of the Golgi apparatus. For example, reaction networks expressed as stochastic and ordinary differential equations have been used to model the distribution of different branching oligosaccharide structures formed by glycosylation, and how this is influenced by the distribution of enzymes within the Golgi compartments [15,29–32]. Other work has used transport modelling or agent-based models to compare competing theories of Golgi maturation [11,33,34], reaction networks to describe the self-organisation and maturation of Golgi compartments by vesicular exchange [35–40], or discrete-element methods [41] and energy minimisation [42–45] to model self-organised membrane structures that recapitulate Golgi morphology. However, the link between Golgi morphology and effective post-translational modification remains (to our knowledge) under-explored.

Fig 1A shows how the Golgi in a trafficking mutant (GMAP210 knockout, as characterized in [20]) is dilated relative to wildtype. The extent of dilation over a population of cells is quantified in Fig 1B. This shows a five-fold variation of maximal cisternal depth within a wildtype population, and an approximate two-fold increase of lumen depth between wildtype and GMAP210 knockout populations. Fig 1C shows the differences in molecular-weight distribution of an example glycosylated cargo, biglycan (BGN), in these cells. Biglycan is a proteoglycan comprised of a core peptide of 40 kilo Da mass modified with two linear glycosaminoglycan (GAG) chains, which increase the mass of BGN to more than 250 kilo Da when fully modified, as seen here in WT cells. Under-modification in KO cells leads to an increase in a 150 kilo Da intermediate. Motivated by the data in Fig 1 (obtained using procedures outlined in [20] and in Supplementary information S1 Text), we explore below the potential relationship between cisternal shape and the molecular-weight profile of a Golgi product, bearing in mind that shape will not be the only determinant of the product's profile.

We model glycosylation within a cisterna as an enzyme-mediated polymerisation reaction (Fig 2 and Eq (S1) in S2 Text). For simplicity, we consider primarily the assembly of linear polysaccharides, best represented biologically by the

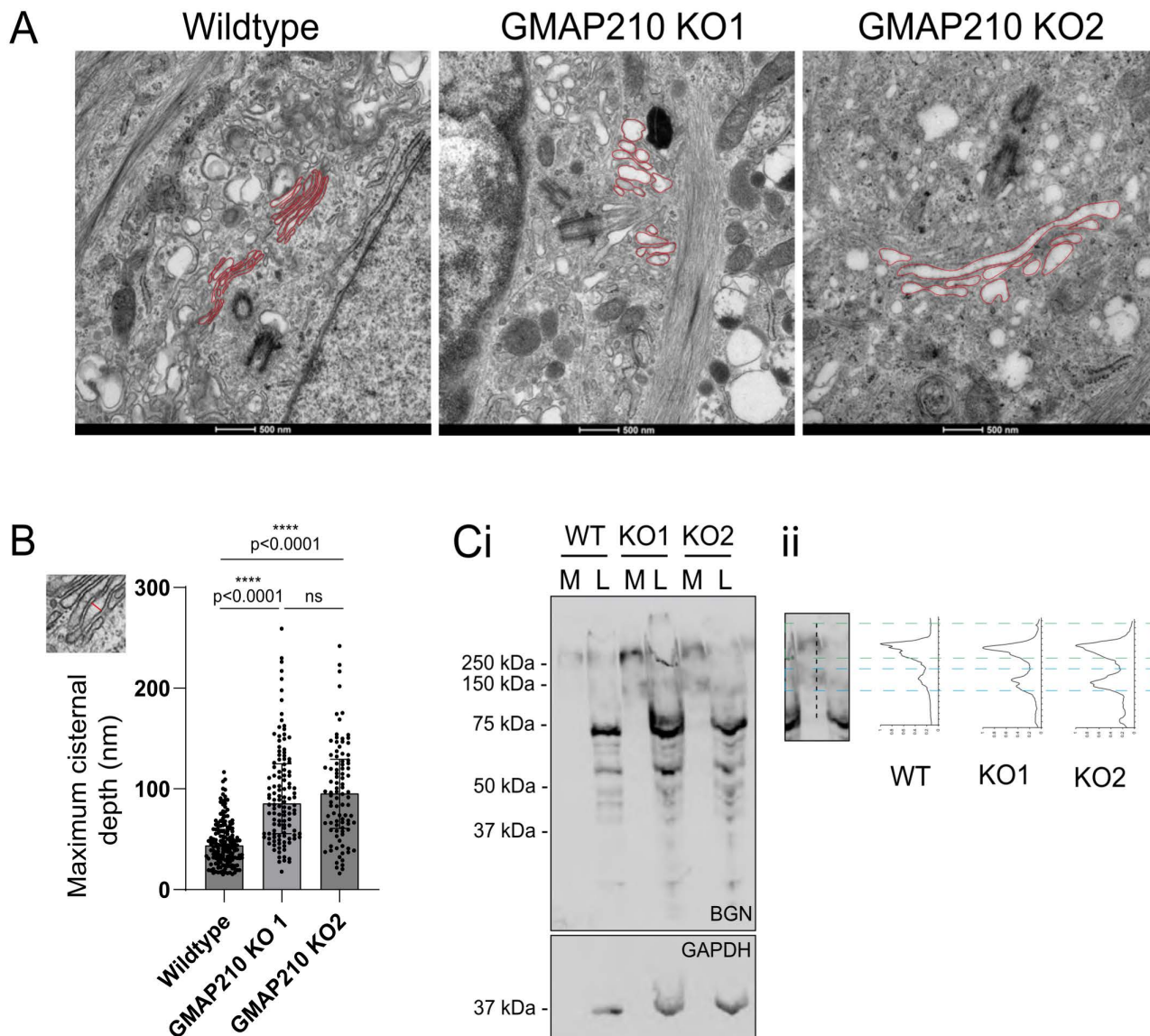


Fig 1. Experimental evidence suggests a link between cisternal dilation and biglycan undermodification in GMAP210 KO cells. (A) Transmission electron micrographs of wildtype (WT) and GMAP210 knockout (KO) RPE1 cells. Golgi membranes are outlined in red. (B) Quantification of the maximal depth of individual cisternae from images represented in A. The inset illustrates a measurement. Each dot represents one cisterna. In total 8-15 cells were measured across two independent experiments. All identifiable cisternae in each cell were measured. Data were analysed with a D'Agostino & Pearson test for normality (failed) and p -values were calculated using a Kruskal Wallis with Dunn's multiple comparisons test. (C)i Western blot of media (M) and lysates (L) collected from cultures of wildtype and GMAP210 KO RPE1 cells stably expressing BGN-SBP-mScarlet-i. Samples were probed with antibodies targeting BGN and GAPDH as a loading control. Two KO clones are presented. (C)ii Line scan profiles of RFP fluorescence intensity through the media lanes of the blot represented in Ci. Green and blue dashed boxes show alignment of intensity peaks with bands on the blot in an example lane and line scan.

<https://doi.org/10.1371/journal.pcbi.1013993.g001>

glycosaminoglycans and as represented in Fig 1. Glycosaminoglycan synthesis initiates with the assembly of a core tetrasaccharide on a serine residue of a cargo peptide. This chain is then extended through the addition of repeating monosaccharide units until the cargo exits the Golgi, with no concurrent polymer trimming [46]. Due to the repetitive nature of this structure, the overall chain length for each polymer is determined by numerous competing factors, such as transport

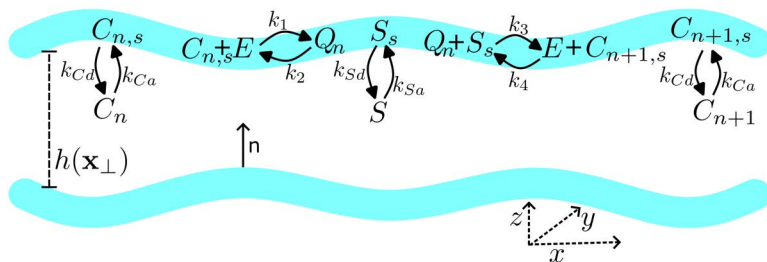


Fig 2. Schematic diagram of the mathematical model. Two cisternal membranes (blue) separate a lumen of thickness $h(\mathbf{x}_\perp)$ where $\mathbf{x}_\perp = (x, y)$; the cisterna lies in the (x, y) -plane and has inward normal $\mathbf{n}$. Substrate molecules S and polymer cargo molecules $C_1, C_2, \dots, C_N$ diffuse freely within the lumen and adsorb reversibly onto the membranes to form membrane-bound substrate S_s and cargo $C_{n,s}$. On each membrane, C_n binds reversibly to membrane-bound enzyme E to form membrane-bound complex Q_n , which then reacts with S_s to form $C_{n+1,s}$, releasing the enzyme E . The cargo $C_{n+1,s}$ is then free to reversibly desorb from the membrane back into the lumen. This system is characterised by 8 separate reaction rates, as labelled in the diagram: k_1 and k_3 (k_2 and k_4) model rates of forward (reverse) polymerization; k_{Ca} and k_{Cd} (k_{Sa} and k_{Sd}) model adsorption and desorption of polymer cargo (substrate).

<https://doi.org/10.1371/journal.pcbi.1013993.g002>

time and enzyme concentration, resulting in the production of a heterogeneous mix of products. The molecular-weight distribution of glycosylated output can therefore provide a sensitive read-out of glycosylation efficiency and its relationship with Golgi conditions including, as relevant here, changes to Golgi structure [13]. The polymer cargo and its monomeric substrate are present in the lumen of the cisterna but react only after adsorbing to a nearby cisternal wall, where a membrane-bound enzyme catalyses addition of a monomer to the polymer. The product of the reaction can desorb back into the lumen and the reaction can repeat. The polymer and substrate move within the lumen by molecular diffusion in a crowded environment. After some time we suppose that the contents of the lumen are released. In the framework illustrated in Fig 2, the resulting polymer cargo distribution can be expected to depend on four surface reaction rates ($k_1, \dots, k_4$), four adsorption/desorption rates of polymer cargo and substrate ($k_{Ca}, k_{Cd}, k_{Sa}, k_{Sd}$), and geometric factors related to the size and shape of the cisterna. We wish to establish in particular how geometric factors may promote or hinder the glycosylation process. The model does not seek to describe other aspects of Golgi function that may influence glycosylation.

Materials and methods

The mathematical model

Full details of the mathematical model are presented in Supplementary information S2 Text. Here we summarise the main assumptions and approximations and introduce the primary variables and parameters. Below, stars denote dimensional quantities.

The model describes adsorption of polymer cargo with luminal concentration C_n^* (where $n = 1, 2, \dots$ describes the polymer length) onto cisternal membranes, where an enzyme-mediated polymerisation step takes place. This is followed by desorption of polymer with length $n + 1$ into the cisternal lumen, following the reaction scheme illustrated in Fig 2 and given in Eq (S1) in S2 Text. The model combines the polymerisation reaction, modelled using mass-action kinetics, with transport by molecular diffusion in the cisternal lumen. The following set of approximations are exploited that permit substantial simplification of the model, facilitating its analysis.

1. The flat and slender geometry of the cisterna, which remains fixed, enables the bulk concentration C_n^* to be represented by a depth-averaged concentration.

2. Adsorption and desorption are assumed to be sufficiently rapid for C_n^* always to be in equilibrium with a surface concentration $C_{n,s}^*$. The affinity of cargo for the surface is captured by a lengthscale $h_C \equiv 2k_{Ca}/k_{Cd}$, a ratio of adsorption rate k_{Ca} to desorption rate k_{Cd} . The factor of 2 is included because two surfaces bound the lumen (Fig 2).
3. The substrate, with luminal concentration S^* , is assumed to be sufficiently abundant for polymerisation not to change S^* appreciably; the substrate is also assumed to adsorb rapidly to the membrane with an affinity captured by a lengthscale $h_S \equiv 2k_{Sa}/k_{Sd}$, a ratio of adsorption rate to desorption rate of substrate.
4. The surface concentration of membrane-bound enzyme, E^* , is assumed to be low enough to be rate-limiting.
5. By assuming that a large number of polymerisation steps take place, and following assumption 2 above, the polymer distributions C_n^* and $C_{n,s}^*$ (with $1 \leq n \leq N$ for some $N \gg 1$, representing a maximum possible polymer length) can be represented by a dimensionless density $\tilde{C}(\nu, \mathbf{x}_\perp, \tilde{t})$ that depends on position $\mathbf{x}_\perp \equiv (x, y)$ in the plane of the cisterna, a dimensionless time $\tilde{t}$ and a continuous variable ν , where $0 \leq \nu \leq 1$, that interpolates n/N .

Expressing the model in dimensionless form, and using thin-layer asymptotics [47] under assumptions 1–2 above, we reduce the diffusion equation in three space dimensions, describing luminal transport of polymer cargo and substrate, to a spatially two-dimensional (2D) diffusion equation that is coupled to a set of ordinary differential equations that describe surface reactions using mass-action kinetics (Eq (S16) in S2 Text). Then, exploiting assumptions 3–5 above, the multiple ordinary differential equations of mass-action kinetics can be combined with the bulk transport equation to recover the following partial differential equation, with polymerisation state represented as a continuous variable ν , coupled to an integral:

$$(1 + \alpha_C h) \partial_{\tilde{t}} \tilde{C} + \tilde{E} \beta \partial_\nu \tilde{C} = \tilde{E} K_2 K_4 \partial_\nu^2 \tilde{C} + \mathcal{D} \nabla_\perp \cdot (h \nabla_\perp \tilde{C}), \quad (1a)$$

$$\tilde{E}(\mathbf{x}_\perp, \tilde{t}) = F_E(\mathbf{x}_\perp) \left[1 + \frac{1}{K_2} \int_0^1 \tilde{C}(\mathbf{x}_\perp, \tilde{t}; \nu) d\nu \right]^{-1}. \quad (1b)$$

This is Eq (S39) in S2 Text; $\partial_{\tilde{t}}$ and ∂_ν denote partial derivatives. Eq (1a) is a non-linear non-local advection-diffusion equation that describes evolution over time $\tilde{t}$ of the concentration field $\tilde{C}(\nu, \mathbf{x}_\perp, \tilde{t})$ due to diffusion in 2D physical space $\mathbf{x}_\perp$ and advection-diffusion in polymerisation space ν . Advection in ν -space (the $\partial_\nu \tilde{C}$ term in Eq (1a)) describes forward progress of the polymerization reaction; diffusion in ν -space (the $\partial_\nu^2 \tilde{C}$ term) accounts for the fact that many different combinations of forward and reverse reaction steps can form a polymer of a given length.

The first term of Eq (1a) represents the rate of change of the combined surface and luminal concentrations; surface reactions are captured by ν derivatives and diffusion in the lumen is represented by the final term in Eq (1a). Since enzyme at any location binds with molecules of any molecular weight, its available (dimensionless) concentration $\tilde{E}$ is given by the integral in Eq (1b). The model accommodates heterogeneities in cisternal depth $h(\mathbf{x}_\perp)$ (via the capacitive prefactor of the time derivative $\partial_{\tilde{t}} \tilde{C}$ and via non-uniform spatial diffusion) and in enzyme distribution (through the prescribed function $F_E(\mathbf{x}_\perp)$ in Eq (1b)), for some given functions h and F_E ; these satisfy the constraints $\int h(\mathbf{x}_\perp) d\mathbf{x}_\perp = \pi$, $\int F_E(\mathbf{x}_\perp) d\mathbf{x}_\perp = \pi$, when integrated over the cisterna. In Eq (1a, 1b), $K_4 = k_4/k_1$; the remaining parameters in Eq (1a, 1b) combine the biochemical rate constants shown in Fig 2 with chemical masses and two geometric quantities (the cisternal volume $|\Omega|$ and its footprint area $|\Omega_\perp|$). Parameters α_C , K_2 , K_4 in Eq (1a, 1b) are defined in Table B in S2 Text; parameters β and $\mathcal{D}$ are defined in Eqs (S34) and (S40) in S2 Text respectively. α_C compares the mean cisternal thickness to the adsorption lengthscale h_C ; the term proportional to $\alpha_C h$ in Eq (1a) represents polymer residing in the cisternal lumen, and is the primary means by which cisternal geometry influences polymerisation rate. $\beta > 0$ in Eq (S34) in S2 Text measures

the strength of the forward polymerisation reaction. The product K_2K_4 measures reverse reaction rates k_2 and k_4 , relative to the forward polymerization rate k_1 , that contribute to dispersion in molecular weight as polymerization proceeds (arising because $\tilde{C}$ describes a population of polymers that are effectively undergoing a biased random walk in v -space). $\mathcal{D}$ in Eq (S40) in [S2 Text](#) measures spatial diffusion in the plane of the cisterna relative to kinetic effects.

Starting with a concentration field derived from a Gaussian distribution with small variance, representing monomeric cargo at $\tilde{t} = 0$, we simulate Eq (1a, 1b) until some release time $\tilde{t} = \tilde{T}_r$. Integration of $\tilde{C}$ over the spatial domain then yields $\tilde{M}(\nu, \tilde{T}_r)$, a distribution of polymer cargo with respect to scaled molecular weight ν at the release time. Treated as a function of ν , $\tilde{M}(\nu, \tilde{T}_r)$ serves as a proxy for the result of a Western blot experiment (as in [Fig 1Cii](#)). We treat the luminal mass of polymer cargo having molecular weight satisfying $0 < \phi < \nu \leq 1$, for some ϕ , as a measure of the functional output of the cisterna. The dimensional mass of luminal polymer cargo having chain length n in the range $\phi N \leq n \leq N$ at time T_r^* is

$$\mathcal{M}_\phi^*(T_r^*) = \frac{\alpha_C \mathcal{C}}{\pi(1 + \alpha_C)} \tilde{M}_\phi(\tilde{T}_r) \quad \text{where} \quad \tilde{M}_\phi(\tilde{T}_r) = \int_\phi^1 \tilde{M}(\nu, \tilde{T}_r) d\nu \quad (2)$$

This is Eq (S44) in [S2 Text](#). Here $\mathcal{C}$ is the initial number of cargo monomers in the cisterna. To quantify cisternal efficiency, we evaluate the time $T_{r,50}^*$ taken to produce 50% of the maximum possible functional output of the reaction, were it allowed to run indefinitely, and define the production rate $\mathcal{P}_{50}^*$ as this functional polymer mass in the cisternal lumen divided by $T_{r,50}^*$ (Eq (S5) in [S2 Text](#)). The primary aim of the model is to explore how different cisternal shapes $h(x, y)$ in [Eq \(1a\)](#), in combination with kinetic parameters, influence the production rate $\mathcal{P}_{50}^*$.

The 17 input parameters of the model (Tables B, C, and D in [S2 Text](#)) include 8 rate constants ([Fig 2](#); Table B in [S2 Text](#)) and three chemical masses per cisterna (of monomer $\mathcal{C}$, substrate $\mathcal{S}$ and enzyme $\mathcal{E}$; Table D in [S2 Text](#); we use the masses $\mathcal{C}$, $\mathcal{S}$ and $\mathcal{E}$ as inputs to the model, rather than the corresponding concentrations). Table H in [S2 Text](#) reports parameter values used in computations. We necessarily make assumptions about the relative sizes of some of these quantities, in order to reduce the model to a tractable and interpretable form. We recognize that direct evidence for many of these assumptions is not currently available and that model predictions must therefore be interpreted cautiously. Values of input parameters in Table H in [S2 Text](#) are given in terms of a nominal reference length $L = 100 \text{ nano m}$ (comparable to a cisternal width, as in [Fig 1B](#)), a time $T = 0.01 \text{ milli s}$ (representative of a desorption rate) and a molecular number $M = 10^3$ (representative of a scarce number of enzyme molecules in a cisterna), that we choose in order to give reasonable outcomes. Time $\tilde{t}$ is scaled as shown in Table D in [S2 Text](#), so that $\tilde{t} = 1$ corresponds to 2 600 s (43 min) for the illustrative parameters chosen in Table H in [S2 Text](#); the spatial coordinate $\mathbf{x}_\perp$ is scaled as shown in Table C in [S2 Text](#); dimensional luminal and surface concentrations are recovered from $\tilde{C}$ via

$$C_n^* = \frac{\alpha_C \mathcal{C}}{|\Omega|(1 + \alpha_C)N} \tilde{C}, \quad C_{n,s}^* = \frac{\mathcal{C}}{\mathcal{A}(1 + \alpha_C)N} \tilde{C}, \quad (3)$$

where $|\Omega|$ is the luminal volume and $\mathcal{A} \equiv 2|\Omega_\perp|$ is the total cisternal membrane area. The simplifications described above substantially reduce the number of independent dimensionless parameters (summarized in the right-hand columns of Tables B and D in [S2 Text](#)), that are implemented in Eq (1a, 1b). In summary, by retaining processes that are likely to be dominant, the model reveals specific dimensionless combinations of parameters that determine outcomes, and provides plausible quantification of the contributions of different physical and chemical processes to glycosylation in a cisterna.

Computational method

A full explanation of computational techniques used to solve Eq (1a, 1b) is provided in Sect [S3](#) in [S2 Text](#), along with code needed to reproduce results in this paper. All numerical results were generated using code written in the Julia

programming language [48], leveraging the `DifferentialEquations.jl` library [49], a strong stability-preserving Runge–Kutta solver [50], the `Makie.jl` plotting library [51], and an incidence matrix approach to differential operators [52]. Unless otherwise specified, parameters as laid out in Table H in S2 Text were used for all results.

Results

While there is uncertainty in the values of many of the input parameters, the model offers predictions of production rate that reveal parameter dependencies and which give insight into factors that promote or hinder functional polymer production.

Depth-dependence of production rate

We first illustrate polymerisation in a cisterna of uniform thickness h_0 (corresponding to a dimensional thickness h_0L), having spatially uniform concentration distributions. (Analytic model predictions for this case are described in Sect S4 in S2 Text.) Fig 3A shows how the polymer cargo concentration distribution, initially monomeric (so that $\tilde{C} = 0$ at $\tilde{t} = 0$ away

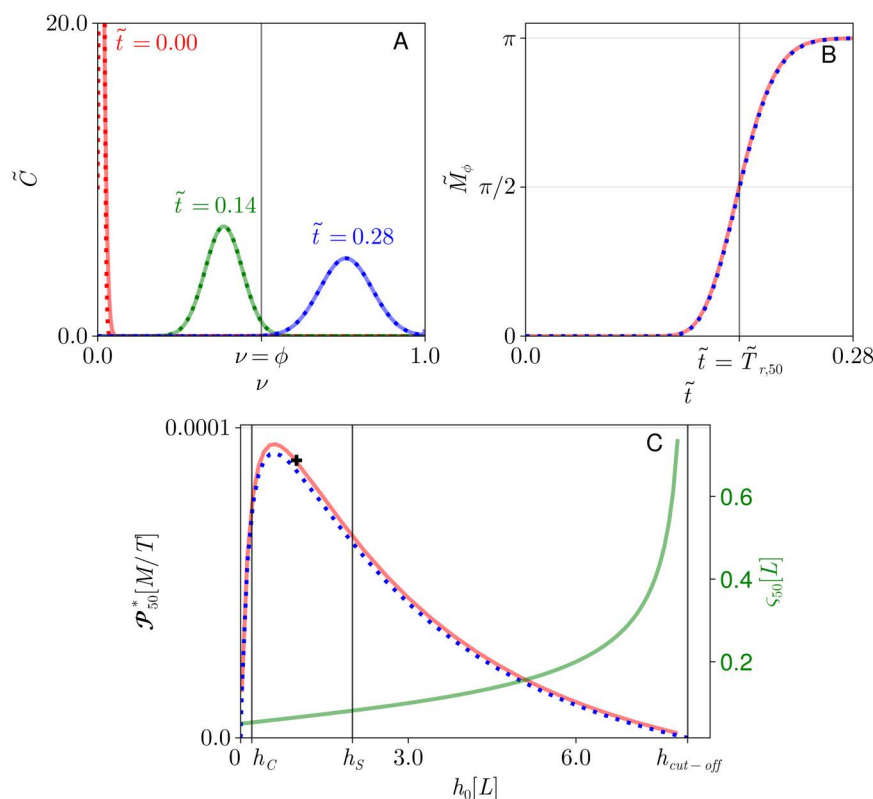


Fig 3. Polymerization in a cisterna of uniform depth. (A) Solutions of Eq (1) assuming uniform cisternal thickness and enzyme distribution, showing dimensionless polymer concentration distribution $\tilde{C}$ versus polymerisation length $\nu = n/N$ at three times, indicated by red, green and blue lines. Numerical solutions (solid lines) are compared to the analytic solution (Eq (S53); dashed lines) with $\tilde{t}_0 = -0.0017$ and $\nu_0 = 0.0080$. The vertical line shows the threshold $\nu = \phi$ above which polymer is treated as functional. (B) Functional polymer production $\tilde{M}_\phi$ (see Eq (2)) against time $\tilde{t}$, comparing the numerical result (solid line) against the analytic result (Eq (S54); dashed line). The time to produce half of the maximum possible production, $\tilde{T}_{r,50}$, is shown. (C) Left axis: Dimensional production rate $\mathcal{P}_{50}^*$ of functional polymer cargo versus cisternal depth h_0 , comparing numerical result (Eq (S50); solid line) to analytic result (Eq (S58); dashed line). h_C and h_S are adsorption depths of cargo and substrate. $h_{\text{cut-off}}$ is given in (5). Right axis: standard deviation ς_{50} of $\tilde{C}$ at $\tilde{t} = \tilde{T}_{r,50}$, from (S71, S72) in S2 Text. Parameters are given in Table H in S2 Text; units of $\mathcal{P}_{50}^*$ and h_0 are given in terms of reference quantities M, L and T. Peak production rates are 0.947×10^{-4} at $h_0 = 0.62$ in numerics, and 0.917×10^{-4} at $h_0 = 0.72$ in analytic expression. The black cross shows the production rate 0.895×10^{-4} at $h_0 = 1$, corresponding to panels A and B.

<https://doi.org/10.1371/journal.pcbi.1013993.g003>

from $\nu = 0$), takes on a Gaussian profile that propagates towards $\nu = 1$ as polymerization proceeds. The mass of functional polymer cargo $\mathcal{M}_\phi^*$ (see Eq (2)) is determined from its dimensionless equivalent $\tilde{\mathcal{M}}_\phi$, which rises from zero to π (Fig 3B) as the $\tilde{C}$ distribution sweeps past $\nu = \phi$, allowing us to identify the half-rise time $\tilde{T}_{r,50}$. (The time $\tilde{t} = 0.2$ translates to approximately 9 minutes, using the parameters in Table H in S2 Text.) $\tilde{T}_{r,50}$ is converted to a dimensional $T_{r,50}^*$ (via Eq (S48)) and used to estimate production rate $\mathcal{P}_{50}^*$, as shown in Fig 3C. The functional polymer production rate magnitude in this example, 0.89×10^{-4} M/T, which is equivalent to approximately 9000 molecules/s for our choice of M and T (see the black cross in Fig 3C), arises from the specific choice of parameter values in Table H in S2 Text. $\mathcal{P}_{50}^*$ can be measured relative to the factor $k_1\mathcal{C}\mathcal{E}/(\mathcal{A}N)$, which reflects the strength of the initial forward reaction and takes the value 10^{-2} M/T = 10^6 molecules/s in this example; here the enzyme concentration is estimated via $\mathcal{E}/\mathcal{A}$. The factor N reflects the requirement for this reaction to repeat many times to form a functional polymer. $k_1\mathcal{C}\mathcal{E}/(\mathcal{A}N)$ overestimates the production rate because the second forward reaction rate k_3 (Fig 2) is small ($k_3 = k_1/40$) in this example (Table H in S2 Text).

A flat cisterna allows the governing partial differential equation to have an analytic solution (Eq (S53) in S2 Text), which agrees closely with simulations (Fig 3A and 3B) after introducing two fitting parameters ($\tilde{t}_0$ and ν_0) linked to details of the initial conditions used in computations. The values of these fitting parameters are very small, so disregarding these corrections, the analysis provides a simple expression for production rate of the form

$$\mathcal{P}_{50}^* = \frac{k_1\mathcal{C}\mathcal{E}}{2\mathcal{A}N\phi} F\left(\frac{h_0}{h_C}, \frac{h_C}{h_S}, \frac{\mathcal{A}k_2}{k_1\mathcal{C}}, \frac{\mathcal{A}k_2}{k_3\mathcal{S}}, \frac{\mathcal{A}k_2k_4}{k_1k_3\mathcal{S}}\right), \quad (4)$$

where the function F is a ratio of polynomials in h_0/h_C (Eq (S58)). The four dimensionless groups that appear as h_0 -independent parameters in F measure the relative adsorption strength of substrate and polymer (h_C/h_S), and their abundances when adsorbed over the total cisternal membrane area $\mathcal{A}$. k_1 and k_3 (k_2 and k_4) are forward (reverse) reaction rates (Fig 2); the reaction requires $\mathcal{A}k_2k_4/k_1k_3\mathcal{S}$ to be sufficiently small in order to proceed. Eq (4) captures the major qualitative features of simulations (Fig 3A and 3B) and reveals direct dependencies of $\mathcal{P}_{50}^*$ on input parameters. We focus here on its variation with cisternal depth, h_0 (Fig 3C).

The production rate initially rises from zero for increasing cisternal depth h_0 (Fig 3C). This is because functional polymer is assumed to reside in the lumen, in equilibrium with that adsorbed onto membranes, and a very thin cisterna accommodates proportionally less functional polymer. The production rate reaches a maximum value as depth increases before falling to zero at a cut-off depth defined by

$$h_{\text{cut-off}} = h_S \left(\frac{Sk_1k_3}{\mathcal{A}k_2k_4} - 1 \right) \quad (5)$$

(Eq (S36) in S2 Text). For $h_{\text{cut-off}}$ to be positive requires the substrate to be sufficiently concentrated on the cisternal membrane, requiring $S/\mathcal{A}$ to exceed the ratio k_2k_4/k_1k_3 between the forward and reverse reaction rates (Fig 2). The cut-off thickness is proportional to the substrate adsorption depth h_S .

Eq (4) can be used to identify the cisternal depth that maximises the production rate. It is helpful to evaluate this optimum in limiting cases. For example, when $h_C \ll h_S$ (as in Fig 3), implying that the polymer adsorbs to the membrane less readily than the substrate, the optimal cisternal thickness can be written

$$h_0 \approx h_C \sqrt{1 + \frac{k_1\mathcal{C}}{\mathcal{A}k_2}}, \quad (6)$$

leading to the maximum production rate given by Eq (S62) in S2 Text. Eq (6) predicts an optimum depth of 0.92 L, consistent (to this level of approximation) with the peaks lying at 0.62 L (solid curve) and 0.72 L (dashed curve) in Fig 3C.

The optimal cisternal thickness in this case is regulated by the adsorption properties of the polymer (h_C), mediated by the abundance of polymer. If, in addition, the cargo is sufficiently abundant, so that the C term dominates in Eq (6), the associated maximum production rate (Eq (S63) in S2 Text) is limited by substrate and enzyme abundance.

Fig 3C also shows how the standard deviation ς_{50} of the $\tilde{C}$ density at $\tilde{t} = \tilde{T}_{r,50}$ (Eqs (S71) and (S72) in S2 Text) grows with cisternal depth, becoming unbounded as h_0 approaches $h_{\text{cut-off}}$. In addition to slowing the reaction, dilution of substrate provides more opportunity for reversals of the polymerization process that disperse the distribution. Thinner cisternae therefore promote a purer product with a more narrowly defined molecular-weight distribution.

In summary, the model (as illustrated by Fig 3) shows how, for a cisterna of uniform depth h_0 , the functional polymer production rate is regulated by cisternal depth: the depth must be below $h_{\text{cut-off}}$ for the substrate to be sufficiently concentrated for the forward reaction to proceed; and the affinities of solute and substrate for the membrane (as expressed by the thicknesses h_C and h_S) determine the thickness at which polymer production proceeds most rapidly. Unfortunately, given current uncertainties in model parameters, it is not possible to make definitive predictions of optimal cisternal depth for specific cargoes; however, expressions such as Eq (6) reveal the factors that regulate optimal width in terms of the dominant biochemical and transport processes.

To illustrate this point, the polynomial structure of the production-rate function F in Eq (4) (see Eq (S58) in S2 Text) allows asymptotic approximations of its maximum value (and the corresponding optimal depth) to be derived across all extremes of its four-dimensional parameter space (Table G in S2 Text). Knowing that F interpolates between these limits, one can then extract local and global parameter dependencies. For example, the limiting optimal cisternal depth is always proportional to an adsorption depth (formed from h_S , h_C or $\sqrt{h_S h_C}$) and the production rate is proportional to $(h_C/h_S)^\alpha$ where $\alpha = 1, 0$ or -1 . When $h_{\text{cut-off}}$ is very small, due to weak substrate adsorption or low substrate levels (see Eq (5)), the optimal depth is approximately half of the cut-off depth (row 1 in Table G in S2 Text), indicating that a doubling in lumen depth may be sufficient to suppress polymerization; more generically, however (rows 2–8), there is a larger gap between the optimum depth and the cut-off, as in Fig 3C (corresponding to row 4 of Table G in S2 Text), enabling polymerization to proceed even after a doubling of lumen depth, providing a degree of robustness. Furthermore, the maximum production rate and optimal lumen depth in a lumen of uniform thickness are independent of the bulk spatial diffusivity, provided it is large enough to ensure cross-luminal mixing.

Dispersion driven by depth and enzyme heterogeneity

There is intrinsic dispersion in the polymerisation process, regulated by biochemical rate constants and evident in Fig 3A. This is captured in the model by the term representing diffusion with respect to v in Eq (1). However, dispersion can also arise from spatial heterogeneities, either in cisternal shape or in enzyme distribution, as illustrated in Fig 4.

To illustrate the role of spatial heterogeneity, we consider a cisterna with a localised region of increased depth, having a profile as shown in Fig 4A. (Here, for illustrative purposes, we consider variation with respect to a single spatial dimension and symmetry in the second dimension; this example is equivalent to a cisterna having a straight ridge of increased thickness.) The two-fold variation in lumen depth in Fig 4A is comparable to variations shown in individual wildtype cisternae in Fig 1A. When Eq (1) is solved for this depth profile and a spatially-uniform initial monomer distribution (Fig 4B), we see significant spatial variation in polymerisation of cargo (Fig 4C and 4D). Since surface-bound polymer is in equilibrium with luminal polymer, the surface reaction leads to changes in the combined population integrated across the cisterna with mass proportional to $(1 + \alpha_C h)\tilde{C}$ per unit area (see the first term in Eq (1a)). It follows that polymerisation proceeds quicker where the cisterna is thinner; equivalently, thicker regions hold more polymer, requiring longer for this polymer to be processed). Integration over space (to obtain $\tilde{M}(\nu, \tilde{t})$) shows how the polymer mass distribution may become bimodal (Fig 4E–4G). The model therefore illustrates how spatial heterogeneity promotes variation in the secreted polymer mass distribution. In contrast, spatial heterogeneity reduces the production rate $\mathcal{P}_{50}^*$ only slightly in this example, from 0.895×10^{-4} (when $h_0 = 1$, as in Fig 3A and 3B) to 0.872×10^{-4} in Fig 4A–4G.

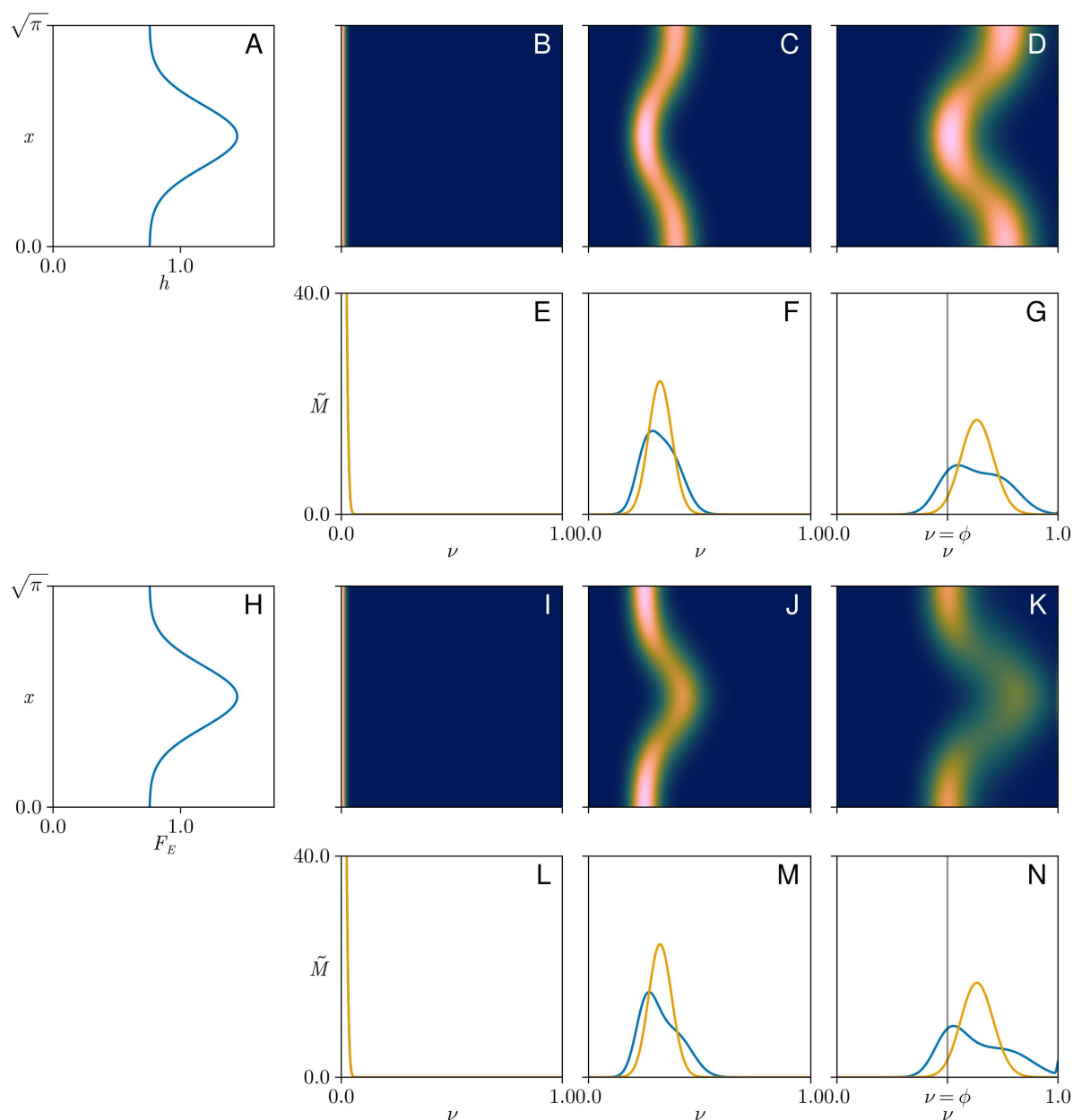


Fig 4. Non-uniformities in one spatial dimension. (A) Dimensionless cysternal thickness $h(x)$ against x showing a Gaussian thickening. (B,C,D) Heatmaps of concentration $\tilde{C}(\nu, x, \tilde{t})$ in real (vertical) and polymerisation (horizontal) space at initial, intermediate, and final states ($\tilde{t} = 0.0, 0.11, 0.22$) associated with the thickness profile in A. (E,F,G) Blue curves: spatial integral of concentration, $\tilde{M}(\nu, \tilde{t})$, corresponding to B-D, versus polymerisation length ν . Orange curves show $\tilde{M}(\nu, \tilde{t})$ when $h = 1$ and $F_E = 1$ uniformly. (H) A prescribed Gaussian enzyme distribution $F_E(x)$ against x . (I,J,K) Heatmaps of concentration $\tilde{C}(\nu, x, \tilde{t})$ in real and polymerisation space at initial, intermediate, and final states ($\tilde{t} = 0.0, 0.11, 0.22$) given the enzyme distribution in (H) and assuming spatially uniform $h(x) = 1$. (L,M,N) Blue curves: spatially integrated concentration distributions, $\tilde{M}(\nu, \tilde{t})$, corresponding to I-K. Orange curves show $\tilde{M}(\nu, \tilde{t})$ when $h = 1$ and $F_E = 1$ uniformly. Parameters are given in Table H in S2 Text. Vertical lines in G, N show the threshold $\nu = \phi$ above which polymer is regarded as functional.

<https://doi.org/10.1371/journal.pcbi.1013993.g004>

A further source of dispersion arises from heterogeneity of enzyme distribution. For example, enzymes have been shown to be preferentially localized towards the cisternal interior, away from cisternal rims [53]. Suppose, therefore, in a cisterna of uniform depth, that there is a region where enzyme is locally enriched, as illustrated in Fig 4H. Since enzyme availability is rate-limiting in the present model, polymerisation proceeds more rapidly in regions of higher enzyme concentration (Fig 4I–4K). Spatial integration leads once again to bimodal polymer mass distributions (Fig 4L–4N), again with a marginal reduction in production rate compared to the uniform case ($\mathcal{P}_{50}^* = 0.846 \times 10^{-4}$, compared to 0.895×10^{-4} when $h_0 = 1$ and $F_E = 1$).

Random domains

The examples in Fig 4 have variation in one spatial dimension but are symmetric in the second spatial dimension, and as such are illustrative of mechanisms but lack the spatial disorder evident in real cisternae. To accommodate this, we simulated polymerisation with depth variation derived from a 2D Gaussian random field [54,55], as shown in Fig 5A. The spatial domain is chosen for convenience to have a square footprint. In the absence of any data suggesting that enzyme abundance correlates with cisternal depth, we assume $F_E = 1$. Numerical integration of Eq (1) gives $\tilde{C}$ as a function of ν ,

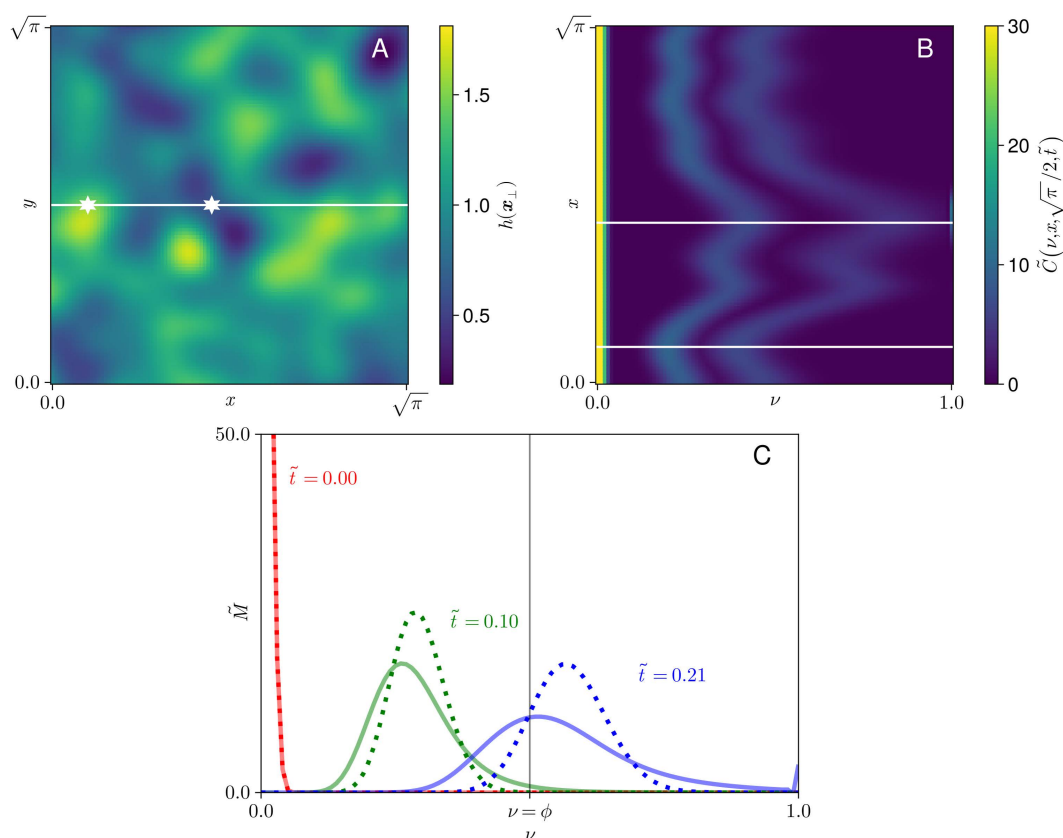


Fig 5. Nonuniformities in two spatial dimensions. (A) Cisternal thickness profile from Gaussian random field with mean 1, standard deviation 0.3, and correlation length 0.2. The white horizontal line shows the slice at $y = \pi/2$ used in panel B; points of minimum and maximum thickness on the line are shown by white stars. (B) Heatmaps of $\tilde{C}(\nu, x, y = \pi/2, \tilde{t})$ at times $\tilde{t} = 0$, $\tilde{t} = 0.10$ and $\tilde{t} = 0.21$; heatmaps are overlaid to demonstrate the evolution of the field. White lines show the locations of minimum and maximum $h(x, y = \pi/2)$, as highlighted in panel B with white stars, corresponding respectively to regions of faster and slower polymerization. (C) Spatial integral $\tilde{M}(\nu, \tilde{t})$ at the same three timepoints shown in panel B, with comparison to the uniform thickness case. The vertical line shows $\nu = \phi$, the threshold above which polymer is regarded as functional. Parameters are given in Table H in S2 Text.

<https://doi.org/10.1371/journal.pcbi.1013993.g005>

$\mathbf{x}_\perp$ and $\tilde{t}$. Visualisation of a scalar field over four dimensions is difficult, so we present projections of the concentration distribution $\tilde{C}$ in Fig 5B. Again, polymerization proceeds more quickly where the cisterna is thinner. The distribution of available enzyme, given by $\tilde{E}$ in Eq (1b), remains almost uniform in this example, varying by less than 2% over the domain at $\tilde{t} = 0.1$, relative to a mean of 0.231. We can further evaluate $\tilde{M}$ and compare to a uniform-depth case with the same parameters, as in Fig 5C. This again demonstrates how spatial variation in cisternal depth leads to a broader distribution of cargo mass.

Discussion

The key conserved feature of Golgi morphology across all species and cell types is the structural flattening of cisternae into thin hollow discs. Such evolutionary conservation highlights this feature as pivotal to the function of the Golgi. The model presented in this study seeks to quantify the relationship between cisternal morphology and some of the biochemical processes underpinning the fundamental role of the Golgi in enzymatic protein modification. We have studied a canonical polymerization process in some simple geometries in order to highlight dominant relationships. Given its fundamental nature, our model may also have relevance to artificial biochemical processing systems such as enzyme-immobilized microfluidic reactors [56–58].

Our strategy has been to reduce the model where possible to simple relationships, deriving explicit relationships that capture prominent features. The 17 input parameters of the full model were reduced to 11 dimensionless ratios by exploiting the small cisternal aspect ratio, and then to 6 dimensionless ratios by a set of additional biochemical assumptions. Despite uncertainties in the values of these quantities, we have been able to draw some noteworthy conclusions. For example, we have demonstrated that, subject to the model's assumptions, an optimal cisternal depth is predicted that maximises the efficiency of useful glycosylation (Fig 3C); the optimal depth depends on biochemical parameters. (The Golgi processes multiple cargoes, so the optimum depth that we have evaluated for one species should be considered alongside the optima for others.) We have also shown that there exists a cut-off depth beyond which polymerisation is not predicted to proceed. Above the optimal depth, thickening of the cisterna leads to dilution of the available substrate, slowing polymerization, until the cut-off depth is reached at which polymerization ceases. These relationships are captured in the rational function F , Eq (4) (see Eq (S58) in S2 Text), which can be interrogated directly or which can be approximated in suitable limits. We illustrated in Eq (6) the optimal thickness when the substrate adsorbs to the membrane more avidly than the polymer cargo, showing how the adsorption depth of the species that adsorbs more weakly to the membrane can be a key determinant of optimal thickness. Equivalent expressions can be derived for other special cases, such as when the substrate adsorbs more weakly to the membrane than the cargo (Eq (S66) in S2 Text). The comprehensive list of asymptotic limits in Table G in S2 Text have the benefit of revealing, transparently, the dominant parameter dependencies of the production rate.

Reversibility of the individual steps in a polymerization reaction, such as those illustrated in Fig 2, leads to dispersion in the molecular-weight profile of polymers sampled at a given time. This dispersion is captured by the v-diffusion term in Eq (1a). In a uniform cisterna, dispersion is predicted to increase dramatically with cisternal depth (Fig 3C) as a result of substrate dilution. (A similar increase in variance is seen also in a model of unregulated filament growth when rates of subunit addition and loss are close in value [59].) We have shown how dispersion is further enhanced in cases of spatial heterogeneity, at least under the assumptions of the model. Polymerisation proceeds more rapidly in thinner regions of the cisterna because, with substrate abundant and enzyme scarce relative to cargo, there is less cargo to process in a given time. Thus, when aggregated over a domain, the overall molecular-weight profile broadens (Fig 5) and can even become bimodal when the domain has distinct thick and thin regions (as illustrated in Fig 4). Furthermore, we found that spatial heterogeneity reduced the production rate of functional polymer. Uniform cisternal thickness therefore promotes both the rate and the quality of glycosylated product, with purer product being achieved in thinner cisternae. Comparing the relatively uniform, thin morphology of wild-type Golgi with more heterogeneous and thicker cisternae of GMAP210 KO cells

(Fig 1A and 1B), the model may explain some of the changes in molecular-weight distribution of glycosylated output from cells with aberrant Golgi (Fig 1C). We emphasise, however, that the depth-dependent mechanism described here is only one of many potential causes of a widened molecular-weight distribution. We showed for example that heterogeneous enzyme distribution can lead to similar outcomes.

The present model rests on numerous assumptions. This is a deliberate compromise, allowing us to capture key processes while maintaining a degree of tractability. Further stages of this work could implement changes to address some of these simplifications and assumptions. For example, we have adopted a simple model of O-glycosylation that ignores numerous complexities [60]. We show in Sect S6 in [S2 Text](#) how the model can be adapted for a peptide with two GAG chains such as biglycan, accommodating the new structure via a doubling of the coefficients of $\tilde{C}_v$ and $\tilde{C}_{vv}$ terms in [Eq \(1a\)](#). Furthermore, we have ignored the possibility that rates of adsorption, desorption, reaction, and diffusion may depend on polymer size. It could be anticipated that longer polymer chains would be less mobile, and therefore less accessible to polymerisation, potentially placing an effective upper limit on polymer length; instead, we have specified an upper bound on polymer length via the parameter N , rather than implementing reaction rates that vary with polymer length [59]. Provided bulk diffusivity is strong enough to promote trans-luminal mixing, and small enough to allow rapid adsorption/desorption kinetics, its impact on predicted production rates is weak (specific constraints are given in Sect S5 in [S2 Text](#)). Numerous additional factors could be addressed, including non-equilibrium adsorption/desorption [61,62], stochastic fluctuations (arising from Brownian effects and small molecular numbers), the role of fenestrations, the off-target impacts of drug treatments affecting other cell biological processes such as Golgi transport, and alternative protein modifications catalysed by membrane-anchored enzymes such as glycan-trimming, sulphation and phosphorylation. We acknowledge that, given the simplifications used here, the conclusions drawn from our model apply primarily to the chemistry taking part in the flattened central areas of the cisternae, and not the cisternal rims where cisternae are often more dilated. We also note that this model takes no account of vesicular trafficking, enzyme recycling, or other features specific to cisternal rims. We believe this approach is valid in light of experimental studies demonstrating the spatial separation of Golgi transport and processing functions to the cisternal rims and flattened domains respectively [53]. Indeed, our findings provide a rationale supporting this model of domain functionalisation within the compartment.

By isolating the contribution of cisternal morphology to regulating Golgi chemistry and output, this model describes one potential method by which the cell optimises glycosylation. To provide more robust mechanistic insight, the predictions described here will need to be tested experimentally. Currently this is challenging with available methodologies. Indeed, we ourselves tested several alternative approaches to alter cisternal depth in vitro, but, as in the case of the GMAP210 knockout lines presented, every method simultaneously disrupted other aspects of Golgi biology that perturbed general secretion or had indirect effects on cell viability. This impeded the collection of material and the interpretation of results. A greater understanding of the machinery maintaining Golgi structure may permit more targeted approaches to be developed in the future. Similarly, the model would be improved by the use of quantitative parameters drawn from experimental data, however we currently lack sufficient knowledge of Golgi chemistry. Recent advances may make this feasible in the near future. The rapid development of super-resolution microscopy techniques [63], and single molecule localisation microscopy [64] may enable the quantification of enzyme concentrations and distribution within membranes. Similarly, fluorescent biosensors are being developed to measure substrates, that could be engineered to measure intra-Golgi concentration [65]. Mathematical models, such as that presented here, help define and prioritise the technological advancements required to better understand this complex organelle experimentally.

In summary, we have presented a mathematical model, inspired by experimental data showing changes in the molecular-weight distribution of glycosylated output from cells with changes in the thickness of their Golgi apparatus, that demonstrates an optimal thickness for glycosylation efficiency, and shows how heterogeneity in Golgi thickness can lead to dispersion in, and hence potentially a reduction in precise control over, the molecular weight of glycosylated cargo.

Supporting information

S1 Text. Supplementary text S1 describes procedures used to generate images in Fig 1.

(PDF)

S2 Text. Supplementary text S2 describes details of the mathematical model. Table A. Concentration fields: variables in the left-hand column are dimensional; the right-hand columns show dimensionless surface concentrations. Gaps in the right-hand columns reflect reduction of model complexity via thin-layer and continuous approximations, given in Sects S2 and S2.2 respectively. **Table B. Rate constants:** the left-hand column shows dimensional parameters, those in the right-hand columns are dimensionless (used in the thin-layer and continuous models of Sects S2 and S2.2). **Table C. Geometric quantities:** dimensional parameters are given in the left-hand column. Dimensionless parameters and variables are given in the right-hand column. **Table D. Biochemical and transport parameters:** dimensionless parameters are given in the right-hand columns. The left-hand column gives dimensional (Dim.) input parameters to the model. The right-hand columns give parameters used in the thin-layer and continuous models given in Sects S2 and S2.2. “Early” concentrations are those arising after the initial concentration field has equilibrated via adsorption to interfaces. The bottom row shows how time is measured in the thin-layer and continuous models. **Table E. Parameter combinations relevant to the production rate (S47).** **Table F. Matrices used in numerical simulations (S50).** **Table G. A summary of the 12 possible asymptotic orderings of the four heights (S67),** arranged as four groups of three cases, showing leading-order approximations of $F_{\max}$, using F in (S58), the leading-order u that maximizes F in the relevant limit, and the corresponding leading-order lumen thickness h . Columns two and four highlight the dependence on adsorption thicknesses h_C and h_S . **Table H. Representative parameter values.** L, T, M are arbitrary units of length, time and molecular number. Small or large parameters can be used to assess the effectiveness of the conditions in the right-hand column that are exploited to simplify the model. $h_{\text{cut-off}}$ is given by (S36). dim. = dimensional, nondim. = nondimensional. **Fig A. Numerical discretisation scheme:** (A) Diagram illustrating discretization of polymerisation space and one spatial dimension. Vertices (green circles labelled by k) and surrounding cuboids discretise the domain. Vertices are connected to their immediate neighbours by directed edges (blue dotted lines labelled by j). For the labels shown, the incidence matrix has elements $A_{jk} = -1$, $A_{jkr} = 1$, $A_{jkr} = -1$. The concentration field C_k is evaluated at vertices and fluxes between vertices are evaluated at edges. (B) Diagram showing discretization of physical space in the case where there is no assumption of uniformity in the second spatial dimension, y . This construction is identical to that used for the first spatial dimension x and polymerisation dimension ν . (C) Diagram showing discretization of physical space in the case where solutions are uniform in the second spatial dimension y . The construction is similar but uses a single row of vertices in y , with Δy being the full range of y . All spatial dimensions are normalised to length $\sqrt{\pi}$.

(PDF)

Author contributions

Conceptualization: Christopher Revell, Martin Lowe, Nicola L. Stevenson, Oliver E. Jensen.

Formal analysis: Christopher Revell, Oliver E. Jensen.

Funding acquisition: Martin Lowe, Oliver E. Jensen.

Investigation: Christopher Revell, Martin Lowe, Nicola L. Stevenson, Oliver E. Jensen.

Methodology: Christopher Revell, Nicola L. Stevenson, Oliver E. Jensen.

Project administration: Christopher Revell, Nicola L. Stevenson, Oliver E. Jensen.

Software: Christopher Revell.

Supervision: Oliver E. Jensen.

Visualization: Christopher Revell.

Writing – original draft: Christopher Revell, Nicola L. Stevenson, Oliver E. Jensen.

Writing – review & editing: Christopher Revell, Martin Lowe, Nicola L. Stevenson, Oliver E. Jensen.

References

- Barlow LD, Nývltová E, Aguilar M, Tachezy J, Dacks JB. A sophisticated, differentiated Golgi in the ancestor of eukaryotes. *BMC Biol.* 2018;16(1):27. <https://doi.org/10.1186/s12915-018-0492-9> PMID: 29510703
- Klute MJ, Melançon P, Dacks JB. Evolution and diversity of the Golgi. *Cold Spring Harb Perspect Biol.* 2011;3(8):a007849. <https://doi.org/10.1101/cshperspect.a007849> PMID: 21646379
- Mowbrey K, Dacks JB. Evolution and diversity of the Golgi body. *FEBS Lett.* 2009;583(23):3738–45. <https://doi.org/10.1016/j.febslet.2009.10.025> PMID: 19837068
- Dacks JB, Davis LAM, Sjögren AM, Andersson JO, Roger AJ, Doolittle WF. Evidence for Golgi bodies in proposed “Golgi-lacking” lineages. *Proc Biol Sci.* 2003;270 Suppl 2(Suppl 2):S168–71. <https://doi.org/10.1098/rsbl.2003.0058> PMID: 14667372
- Alberts B. *Molecular Biology of the Cell.* 5 ed. Garland Science. 2008.
- Lowe M. Structural organization of the Golgi apparatus. *Curr Opin Cell Biol.* 2011;23(1):85–93. <https://doi.org/10.1016/j.ceb.2010.10.004> PMID: 21071196
- Nakamura N, Wei J-H, Seemann J. Modular organization of the mammalian Golgi apparatus. *Curr Opin Cell Biol.* 2012;24(4):467–74. <https://doi.org/10.1016/j.ceb.2012.05.009> PMID: 22726585
- Klumperman J. Architecture of the mammalian Golgi. *Cold Spring Harb Perspect Biol.* 2011;3(7):a005181. <https://doi.org/10.1101/cshperspect.a005181> PMID: 21502307
- Dunlop MH, Ernst AM, Schroeder LK, Toomre DK, Lavieu G, Rothman JE. Land-locked mammalian Golgi reveals cargo transport between stable cisternae. *Nat Commun.* 2017;8(1):432. <https://doi.org/10.1038/s41467-017-00570-z> PMID: 28874656
- Glick BS, Nakano A. Membrane traffic within the Golgi apparatus. *Annu Rev Cell Dev Biol.* 2009;25:113–32. <https://doi.org/10.1146/annurev-cell-bio.24.110707.175421> PMID: 19575639
- Dmitrieff S, Rao M, Sens P. Quantitative analysis of intra-Golgi transport shows intercisternal exchange for all cargo. *Proc Natl Acad Sci U S A.* 2013;110(39):15692–7. <https://doi.org/10.1073/pnas.1303358110> PMID: 24019488
- Yarwood R, Hellicar J, Woodman PG, Lowe M. Membrane trafficking in health and disease. *Dis Model Mech.* 2020;13(4):dmm043448. <https://doi.org/10.1242/dmm.043448> PMID: 32433026
- Hellicar J, Stevenson NL, Stephens DJ, Lowe M. Supply chain logistics - the role of the Golgi complex in extracellular matrix production and maintenance. *J Cell Sci.* 2022;135(1):jcs.258879. <https://doi.org/10.1242/jcs.258879> PMID: 35023559
- Stevenson NL. The factory, the antenna and the scaffold: the three-way interplay between the Golgi, cilium and extracellular matrix underlying tissue function. *Biol Open.* 2023;12(2):bio059719. <https://doi.org/10.1242/bio.059719> PMID: 36802341
- Fisher P, Ungar D. Bridging the Gap between Glycosylation and Vesicle Traffic. *Front Cell Dev Biol.* 2016;4:15. <https://doi.org/10.3389/fcell.2016.00015> PMID: 27014691
- Glick BS. Cell biology: alternatives to baker's yeast. *Curr Biol.* 1996;6(12):1570–2. [https://doi.org/10.1016/s0960-9822\(02\)70774-4](https://doi.org/10.1016/s0960-9822(02)70774-4) PMID: 8994815
- Benvenuto G, Leone S, Astoricchio E, Bormke S, Jasek S, D'Aniello E, et al. Evolution of the ribbon-like organization of the Golgi apparatus in animal cells. *Cell Rep.* 2024;43(3):113791. <https://doi.org/10.1016/j.celrep.2024.113791> PMID: 38428420
- Dippold HC, Ng MM, Farber-Katz SE, Lee S-K, Kerr ML, Peterman MC, et al. GOLPH3 bridges phosphatidylinositol-4- phosphate and actomyosin to stretch and shape the Golgi to promote budding. *Cell.* 2009;139(2):337–51. <https://doi.org/10.1016/j.cell.2009.07.052> PMID: 19837035
- Smits P, Bolton AD, Funari V, Hong M, Boyden ED, Lu L, et al. Lethal skeletal dysplasia in mice and humans lacking the golgin GMAP-210. *N Engl J Med.* 2010;362(3):206–16. <https://doi.org/10.1056/NEJMoa0900158> PMID: 20089971
- Thompson G, Hoyle A, Lewis PA, Prada-Sanchez ME, Swift J, Heesom K, et al. Multiple golgins are required to support extracellular matrix secretion, modification, and assembly. *J Cell Biol.* 2025;224(10):e202411167. <https://doi.org/10.1083/jcb.202411167> PMID: 40824304
- Sato K, Roboti P, Mironov AA, Lowe M. Coupling of vesicle tethering and Rab binding is required for in vivo functionality of the golgin GMAP-210. *Mol Biol Cell.* 2015;26(3):537–53. <https://doi.org/10.1091/mbc.E14-10-1450> PMID: 25473115
- Wehrle A, Witkos TM, Unger S, Schneider J, Folliot JA, Hermann J, et al. Hypomorphic mutations of TRIP11 cause odontochondrodysplasia. *JCI Insight.* 2019;4(3):e124701. <https://doi.org/10.1172/jci.insight.124701> PMID: 30728324
- Yamaguchi H, Meyer MD, He L, Senavirathna L, Pan S, Komatsu Y. The molecular complex of ciliary and golgin protein is crucial for skull development. *Development.* 2021;148(13):dev199559. <https://doi.org/10.1242/dev.199559> PMID: 34128978
- Holappa K, Muñoz MT, Egea G, Kellokumpu S. The AE2 anion exchanger is necessary for the structural integrity of the Golgi apparatus in mammalian cells. *FEBS Lett.* 2004;564(1–2):97–103. [https://doi.org/10.1016/S0014-5793\(04\)00315-1](https://doi.org/10.1016/S0014-5793(04)00315-1) PMID: 15094048

25. Lázaro-Díéguez F, Jiménez N, Barth H, Koster AJ, Renau-Piqueras J, Llopis JL, et al. Actin filaments are involved in the maintenance of Golgi cisternae morphology and intra-Golgi pH. *Cell Motil Cytoskeleton*. 2006;63(12):778–91. <https://doi.org/10.1002/cm.20161> PMID: 16960891
26. Frappalo A, Karimpour-Ghahnavieh A, Sechi S, Giansanti MG. The Close Relationship between the Golgi Trafficking Machinery and Protein Glycosylation. *Cells*. 2020;9(12):2652. <https://doi.org/10.3390/cells9122652> PMID: 33321764
27. Schjoldager KT, Narimatsu Y, Joshi HJ, Clausen H. Global view of human protein glycosylation pathways and functions. *Nat Rev Mol Cell Biol*. 2020;21(12):729–49. <https://doi.org/10.1038/s41580-020-00294-x> PMID: 33087899
28. Colley KJ, Varki A, Haltiwanger RS, Kinoshita T. Cellular organization of glycosylation. In: Varki A, Cummings RD, Esko JD, Stanley P, Hart GW, Aebi M, et al., editors. *Essentials of glycobiology*. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press. p. 43–52. <https://doi.org/10.1101/glycobiology.4e.4>
29. Fisher P, Spencer H, Thomas-Oates J, Wood AJ, Ungar D. Modeling Glycan Processing Reveals Golgi-Enzyme Homeostasis upon Trafficking Defects and Cellular Differentiation. *Cell Rep*. 2019;27(4):1231–1243.e6. <https://doi.org/10.1016/j.celrep.2019.03.107> PMID: 31018136
30. Fisher P, Thomas-Oates J, Wood AJ, Ungar D. The N-Glycosylation Processing Potential of the Mammalian Golgi Apparatus. *Front Cell Dev Biol*. 2019;7:157. <https://doi.org/10.3389/fcell.2019.00157> PMID: 31457009
31. Jaiman A, Thattai M. Golgi compartments enable controlled biomolecular assembly using promiscuous enzymes. *Elife*. 2020;9:e49573. <https://doi.org/10.7554/eLife.49573> PMID: 32597757
32. Puri A, Neelamegham S. Understanding glycomechanics using mathematical modeling: a review of current approaches to simulate cellular glycosylation reaction networks. *Ann Biomed Eng*. 2012;40(4):816–27. <https://doi.org/10.1007/s10439-011-0464-5> PMID: 22090146
33. Quiros DN, Nieto F, Mayorga LS. From cartoons to quantitative models in Golgi transport. *Biol Cell*. 2021;113(3):146–64. <https://doi.org/10.1111/boc.202000107> PMID: 33275796
34. Mani S, Thattai M. Stacking the odds for Golgi cisternal maturation. *Elife*. 2016;5:e16231. <https://doi.org/10.7554/eLife.16231> PMID: 27542195
35. Vagne Q, Sens P. Stochastic Model of Maturation and Vesicular Exchange in Cellular Organelles. *Biophys J*. 2018;114(4):947–57. <https://doi.org/10.1016/j.bpj.2017.12.018> PMID: 29490254
36. Vagne Q, Sens P. Stochastic Model of Vesicular Sorting in Cellular Organelles. *Phys Rev Lett*. 2018;120(5):058102. <https://doi.org/10.1103/PhysRevLett.120.058102> PMID: 29481197
37. Vagne Q, Vrel J-P, Sens P. A minimal self-organisation model of the Golgi apparatus. *Elife*. 2020;9:e47318. <https://doi.org/10.7554/eLife.47318> PMID: 32755543
38. Gong H, Sengupta D, Linstedt AD, Schwartz R. Simulated de novo assembly of golgi compartments by selective cargo capture during vesicle budding and targeted vesicle fusion. *Biophys J*. 2008;95(4):1674–88. <https://doi.org/10.1529/biophysj.107.127498> PMID: 18469086
39. Heinrich R, Rapoport TA. Generation of nonidentical compartments in vesicular transport systems. *J Cell Biol*. 2005;168(2):271–80. <https://doi.org/10.1083/jcb.200409087> PMID: 15657397
40. Sachdeva H, Barma M, Rao M. Nonequilibrium description of de novo biogenesis and transport through Golgi-like cisternae. *Sci Rep*. 2016;6:38840. <https://doi.org/10.1038/srep38840> PMID: 27991496
41. Kühnle J, Shillcock J, Mouritsen OG, Weiss M. A modeling approach to the self-assembly of the Golgi apparatus. *Biophys J*. 2010;98(12):2839–47. <https://doi.org/10.1016/j.bpj.2010.03.035> PMID: 20550896
42. Tachikawa M, Mochizuki A. Golgi apparatus self-organizes into the characteristic shape via postmitotic reassembly dynamics. *Proc Natl Acad Sci U S A*. 2017;114(20):5177–82. <https://doi.org/10.1073/pnas.1619264114> PMID: 28461510
43. Tachikawa M. Theoretical approaches for understanding the self-organized formation of the Golgi apparatus. *Dev Growth Differ*. 2023;65(3):161–6. <https://doi.org/10.1111/dgd.12842> PMID: 36718582
44. Derganc J, Mironov AA, Svetina S. Physical factors that affect the number and size of Golgi cisternae. *Traffic*. 2006;7(1):85–96. <https://doi.org/10.1111/j.1600-0854.2005.00365.x> PMID: 16445689
45. Jelerčič U. Mechanical model of Golgi apparatus. *Phys Biol*. 2019;16(6):066003. <https://doi.org/10.1088/1478-3975/ab3766> PMID: 31365910
46. Prydz K. Determinants of Glycosaminoglycan (GAG) Structure. *Biomolecules*. 2015;5(3):2003–22. <https://doi.org/10.3390/biom5032003> PMID: 26308067
47. Jensen OE, Grotberg JB. The spreading of heat or soluble surfactant along a thin liquid film. *Physics of Fluids A: Fluid Dynamics*. 1993;5(1):58–68. <https://doi.org/10.1063/1.858789>
48. Bezanson J, Edelman A, Karpinski S, Shah VB. Julia: A Fresh Approach to Numerical Computing. *SIAM Rev*. 2017;59(1):65–98. <https://doi.org/10.1137/141000671>
49. Rackauckas C, Nie Q. DifferentialEquations.jl – A Performant and Feature-Rich Ecosystem for Solving Differential Equations in Julia. *JORS*. 2017;5(1):15. <https://doi.org/10.5334/jors.151>
50. Gottlieb S, Ketcheson DI, Shu C-W. High Order Strong Stability Preserving Time Discretizations. *J Sci Comput*. 2008;38(3):251–89. <https://doi.org/10.1007/s10915-008-9239-z>
51. Danisch S, Krumbiegel J. Makie.jl: Flexible high-performance data visualization for Julia. *JOSS*. 2021;6(65):3349. <https://doi.org/10.21105/joss.03349>

52. Grady LJ, Polimeni JR. Discrete Calculus. Springer London. 2010. <https://doi.org/10.1007/978-1-84996-290-2>
53. Tie HC, Ludwig A, Sandin S, Lu L. The spatial separation of processing and transport functions to the interior and periphery of the Golgi stack. *Elife*. 2018;7:e41301. <https://doi.org/10.7554/eLife.41301> PMID: [30499774](https://pubmed.ncbi.nlm.nih.gov/30499774/)
54. Lord GJ, Powell CE, Shardlow T. An introduction to computational stochastic PDEs. Cambridge University Press. 2014. <https://doi.org/10.1017/cbo9781139017329>
55. Graham IG, Kuo FY, Nuyens D, Scheichl R, Sloan IH. Analysis of Circulant Embedding Methods for Sampling Stationary Random Fields. *SIAM J Numer Anal*. 2018;56(3):1871–95. <https://doi.org/10.1137/17m1149730>
56. Zhu Y, Chen Q, Shao L, Jia Y, Zhang X. Microfluidic immobilized enzyme reactors for continuous biocatalysis. *React Chem Eng*. 2020;5(1):9–32. <https://doi.org/10.1039/c9re00217k>
57. Patil PD, Gargate N, Dongarsane K, Jagtap H, Phirke AN, Tiwari MS, et al. Revolutionizing biocatalysis: A review on innovative design and applications of enzyme-immobilized microfluidic devices. *Int J Biol Macromol*. 2024;281(Pt 1):136193. <https://doi.org/10.1016/j.ijbiomac.2024.136193> PMID: [39362440](https://pubmed.ncbi.nlm.nih.gov/39362440/)
58. Holyavka MG, Artyukhov VG. Prospects and problems in enzyme immobilization methodology: comprehensive review. *Biophys Rev*. 2025;17(5):1471–509. <https://doi.org/10.1007/s12551-025-01360-4> PMID: [41613885](https://pubmed.ncbi.nlm.nih.gov/41613885/)
59. Mohapatra L, Goode BL, Jelenkovic P, Phillips R, Kondev J. Design Principles of Length Control of Cytoskeletal Structures. *Annu Rev Biophys*. 2016;45:85–116. <https://doi.org/10.1146/annurev-biophys-070915-094206> PMID: [27145876](https://pubmed.ncbi.nlm.nih.gov/27145876/)
60. Krambeck FJ, Betenbaugh MJ. A mathematical model of N-linked glycosylation. *Biotechnol Bioeng*. 2005;92(6):711–28. <https://doi.org/10.1002/bit.20645> PMID: [16247773](https://pubmed.ncbi.nlm.nih.gov/16247773/)
61. Weyer H, Roth TA, Frey E. Protein pattern morphology and dynamics emerging from effective interfacial tension. *Nat Phys*. 2025;22(1):94–102. <https://doi.org/10.1038/s41567-025-03101-6>
62. Burkart T, Müller BJ, Frey E. Dimensionality reduction in bulk-boundary reaction-diffusion systems. *Phys Rev E*. 2024;110(3–1):034412. <https://doi.org/10.1103/PhysRevE.110.034412> PMID: [39425305](https://pubmed.ncbi.nlm.nih.gov/39425305/)
63. Tie HC, Mahajan D, Lu L. Visualizing intra-Golgi localization and transport by side-averaging Golgi ministacks. *J Cell Biol*. 2022;221(6):e202109114. <https://doi.org/10.1083/jcb.202109114> PMID: [35467701](https://pubmed.ncbi.nlm.nih.gov/35467701/)
64. Lelek M, Gyparakis MT, Beliu G, Schueder F, Griffié J, Manley S, et al. Single-molecule localization microscopy. *Nat Rev Methods Primers*. 2021;1:39. <https://doi.org/10.1038/s43586-021-00038-x> PMID: [35663461](https://pubmed.ncbi.nlm.nih.gov/35663461/)
65. Li Z, Zhang J, Ai H-W. Genetically encoded green fluorescent biosensors for monitoring UDP-GlcNAc in live cells. *ACS Cent Sci*. 2021;7(10):1763–70. <https://doi.org/10.1021/acscentsci.1c00745> PMID: [34729420](https://pubmed.ncbi.nlm.nih.gov/34729420/)