Multiscale Continuum Modeling of Prion Dynamics in Dividing Yeast Cells

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What Are Prions?

Prions are proteins capable of misfolding and aggregating. These aggregates then serve as templates for further misfolding and may be fragmented, thus amplifying the aggregation dynamics. Prion diseases (such as Creutzfeldt-Jakob and fatal familial insomnia) are universally progressive and fatal. These aggregation processes also underlie other neurodegenerative diseases such Alzheimer's, and Parkinson's Disease.

Why Study Prions in Yeast?

Prion aggregates are not harmful in yeast (unlike in mammals) and the aggregation dynamics are influenced by asymmetric cell division, which causes an unequal distribution between mother and daughter cells, as shown in Fig. 1.
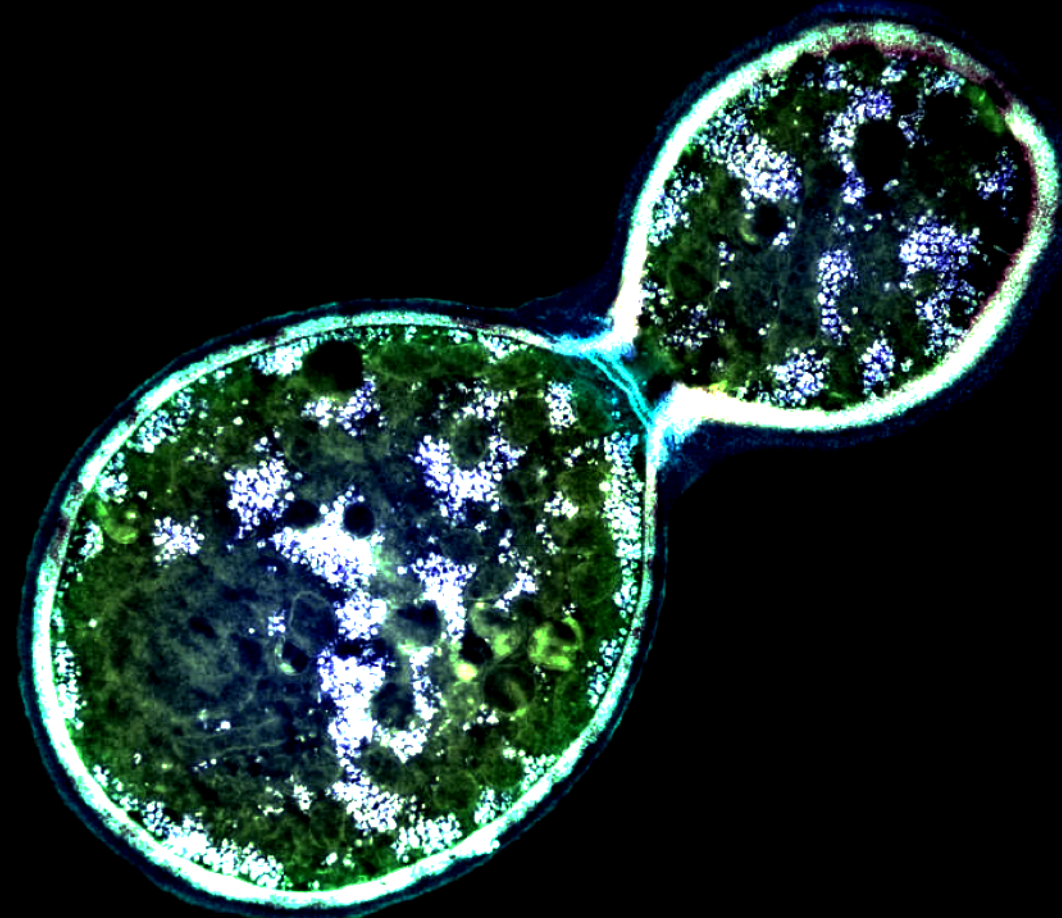

Figure 1: A yeast cell dividing asymmetrically . The mother (Left) is larger than the daughter (Right) [1]

Our Contribution

1. 3D Model of Protein Aggregation
2. General 3D Solver for a dividing cell
3. Critical thresholds for Diffusion and Reaction

Our Reaction-Diffusion Model of Protein Aggregation

We model the aggregation process for two species A, B with two key features:
1) The species can diffuse freely in space 2) Both species can convert to one another, such that $A + A \rightarrow B$
These yield the following reaction diffusion system:

$$(1) \quad \partial_t \psi_A - D_A \Delta \psi_A = 2\gamma \psi_B - \beta \psi_A^2$$

$$(2) \quad \partial_t \psi_B - D_B \Delta \psi_B = \frac{1}{2}\beta \psi_A^2 - \gamma \psi_B$$

where β, γ are the conversion rates and ψ_A, ψ_B are the concentrations for A, B respectively. For now, our model assumes no creation or annihilation of either species.

Simulation of the Dividing Yeast Cell

Our first goal was to verify asymmetric distribution of biochemical species with slow diffusion for our coupled reaction-diffusion model Eq. (1-2), which is illustrated in Figure 2.
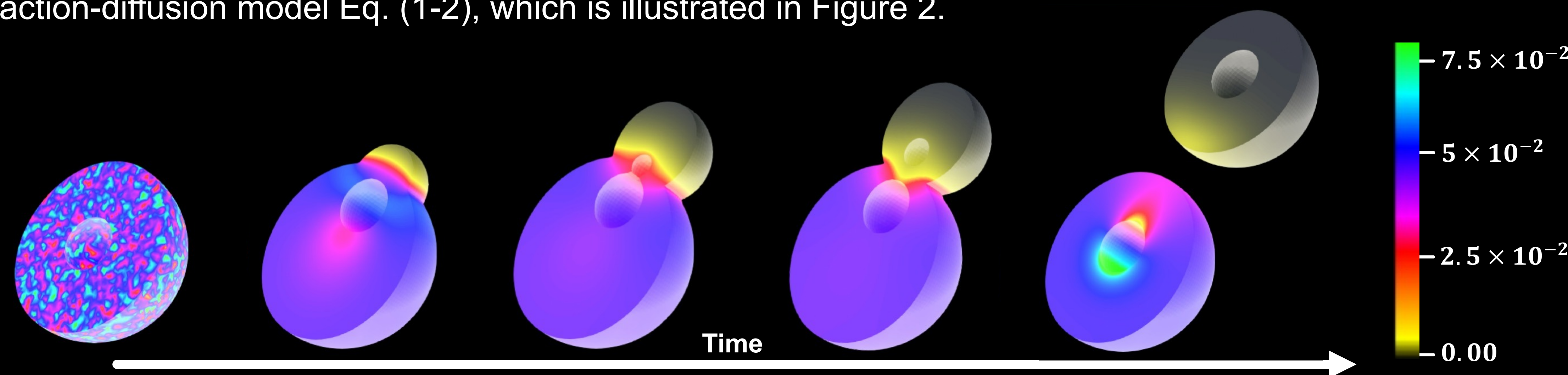

Figure 2: Time-course of ψ_A in the dividing yeast cell with a dividing nucleus shows asymmetric protein distribution.

We next studied the final concentration in the daughter cell under varying diffusion rates ($\beta = \gamma = 0$) (Fig. 3a) and various rates of β under fixed non-critical diffusion rate and $\gamma = 0$ (Fig 3b).
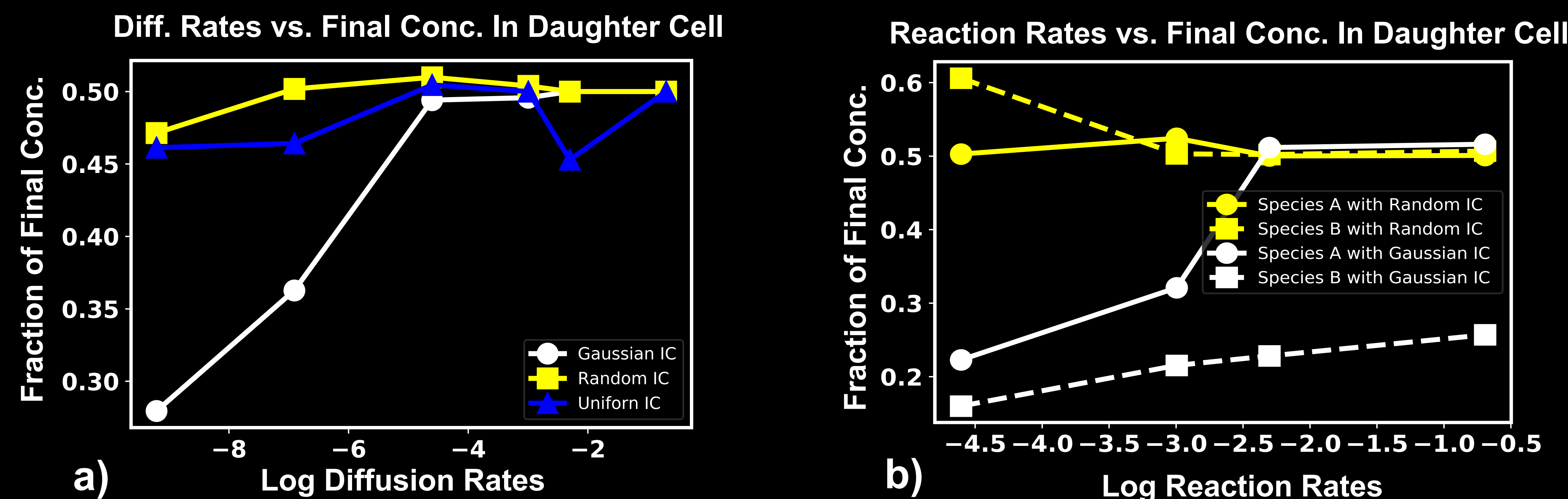

Figure 3: a) Final concentration in daughter cell differs noticeably for smaller diffusion rates with Gaussian initial condition (IC) vs random and uniform IC. Our critical diffusion rates match with an ODE diffusion system with similar parameters by Kinkhabwala et al. [3] b) Final concentration of the reacting species with Gaussian IC increases significantly for larger reaction rates in contrast to the system with random IC.

Level Set Based Solver

Since the daughter cell grows from the mother cell, we have a changing interface (Fig 2). We use the level set (LS) [2] method to find an implicit representations of the dividing cell by taking the LS function of the mother, ϕ_m, and the daughter cell, ϕ_d, which is $\phi = \min(\phi_m, \phi_d)$
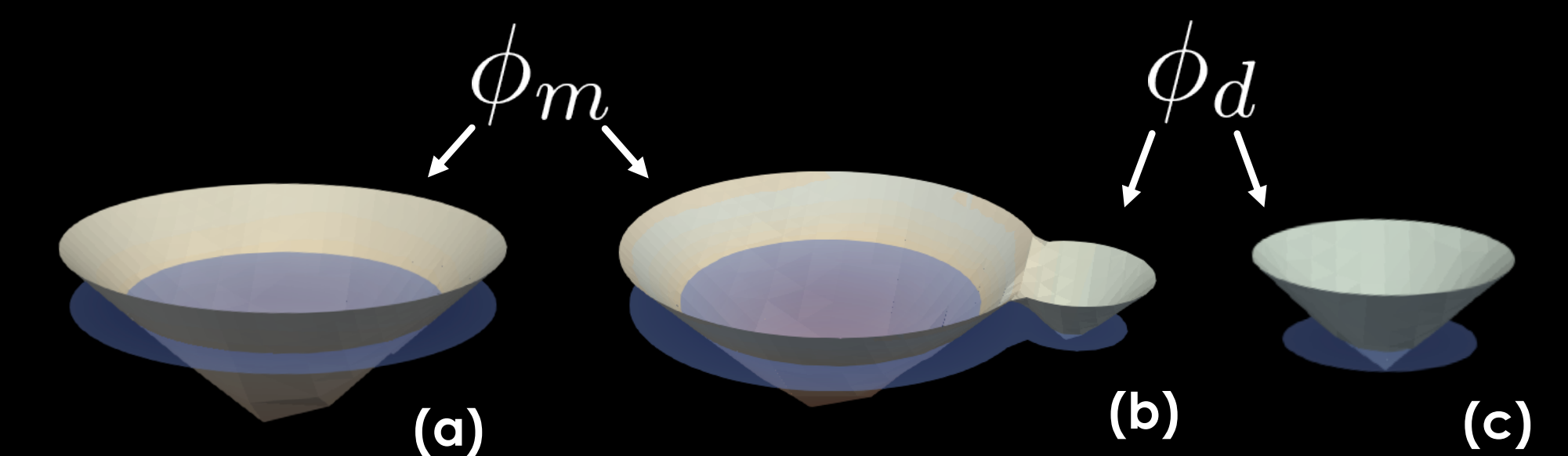

Figure 4: LS representation of the 2D mother cell (a), 2D daughter cell (b) and intersection of both (b)

Our cases are:

(1) $\phi(x, y, z) < 0 \implies$ Inside the biological cell

(2) $\phi(x, y, z) > 0 \implies$ Outside the biological cell

(3) $\phi(x, y, z) = 0 \implies$ On the boundary

Summary

We introduce the first mathematically consistent formulation explaining bias in the size distributions between dividing cells. Furthermore, our work provides a framework for studying more complex and biologically relevant intracellular dynamics, which can provide insight into treating protein-related diseases such as Alzheimer's, Creutzfeldt-Jakob and fatal familial insomnia.

Acknowledgments

References

Simulations