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Fusion leads to effective segregation of damage during cell division: An analytical treatment

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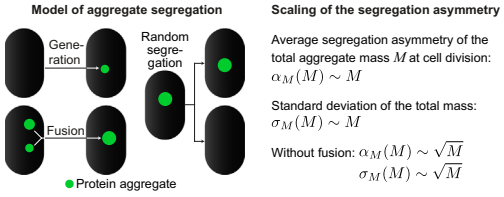
HIGHLIGHTS

- Fusion of aggregates in dividing cells studied analytically.
- Dependence of damage segregation on parameters of aggregation processes obtained.
- Fusion can be as effective as directed transport for damage partition.

GRAPHICAL ABSTRACT



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ABSTRACT

High levels of cellular damage are associated with impairment of cellular function and cell death. Partitioning the damage into a fraction of cells in the population improves population fitness and survival. We have previously shown that protein aggregates, resulting from misfolded, damaged proteins, fuse with each other leading to damage partitioning during cell division. Here, using an analytical treatment of aggregate fusion in dividing cells we present analytical expressions for two measures of damage partition: aggregate mass partition asymmetry between two dividing cells and standard deviation of total aggregate mass across the population. The scaling laws obtained demonstrate how damage partition may generally depend on characteristics of the cellular processes, facilitating better understanding of damage segregation in biological cells.

1. Introduction

High levels of aggregates, which can arise due to stress, have been shown to lead to impairment of cellular function in the model unicellular organisms *Escherichia coli* (Lindner et al., 2008) and the budding yeast *Saccharomyces cerevisiae* (Aguilaniu et al., 2003), and even to cell death in the fission yeast *Schizosaccharomyces pombe* (Coelho et al., 2013). These cells display mechanisms for damage partition that produce a fraction of the population with higher than usual damage levels, in doing so leaving another fraction with lower than usual damage levels, which can improve the overall viability of the cell population. In *S. cerevisiae*, aggregates are retained by the mother cell due to limited diffusion through the narrow neck connecting dividing cells (Zhou et al., 2011), due to tethering to organellar structures (Liu et al., 2010; Spokoini et al., 2012; Zhou et al., 2014) and by directed transport of aggregates from the bud to the mother (Liu et al., 2010). In *E. coli*, aggregate levels correlate with the oldest cell pole inherited by a daughter (Lindner et al., 2008) and in *S. pombe* after stress, fusion between aggregates generates a single large aggregate that is retained only by one of the daughter cells (Coelho et al., 2014). Damage partitioning is not beneficial under favourable conditions compared to repairing the damage, but partitioning becomes crucial for survival under stress, where the rate of damage accumulation is high (Clegg et al., 2014).

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The central aim of the present paper is to demonstrate analytically that fusion of aggregates in a population of dividing cells is also an effective strategy for partitioning damage into a fraction of cells in the population. The analytical findings obtained here complement our recent experimental and numerical results for the symmetrically dividing fission yeast *S. pombe* (Coelho et al., 2014), in which such a fusion-driven segregation was found. Qualitatively, damage partition proceeds by rapid fusion of aggregates into a small number of large aggregates, leading to a significant fraction of the aggregate mass being unable to be split between the daughter cells at division.

We develop a minimal model for aggregation dynamics in a population of dividing cells. In contrast to recent work that models spatial diffusion of individual aggregates (Zhou et al., 2011) or total aggregate levels per cell (Erjavec et al., 2008), the minimal model presented here occupies a middle ground, operating on a non-spatially explicit size distribution of aggregates in each cell. The key results are analytical expressions for two measures of damage partition, namely average segregation asymmetry of aggregate mass at a single cell division, $\alpha_M(M)$, and standard deviation in total aggregate mass per cell across a population, $\sigma_M(M)$. Here M is the total aggregate mass, an indicator of overall stress level.

In particular, the manner in which these damage partition measures scale with M is studied, in order to understand how the damage partition mechanism deals with increased stress. A stronger scaling class, that is, a stronger dependence on M, indicates a greater ability to partition damage at high stress levels, which is precisely where effective damage partition is most necessary. Remarkably, in each of the partition mechanisms studied here the two measures always have the same scaling.

The minimal model, which is treated analytically, and a numerical model are first introduced and defined in Section 2. Analytical mean-field results for the size distributions are obtained in Section 3, including exact results for the stationary distribution and non-stationary low-order moments. This leads to the first measure of damage partition, average segregation asymmetry of aggregate mass at cell division. The second measure requires the van Kampen system size expansion in Section 4. Possible extensions to the model such as 'leakage' and directed transport, which may more accurately represent aggregate dynamics in other unicellular organisms, are considered in Section 5, followed by concluding remarks in Section 6.

2. Model

Aggregation processes, which have been subject to mathematical study for nearly a century (Smoluchowski, 1916; Drake et al., 1972; Aldous, 1999; Wattis, 2006; Lushnikov, 2006), have played long-standing and crucial roles in a wide variety of physical disciplines, including planet formation (Safronov, 1969), atmospheric physics (Pruppacher and Klett, 1980) and industrial colloids (Jones and Pusey, 1991). The same mathematical approaches can be used to study aggregation processes in many important biological contexts, at levels from social group formation (Gueron and Levin, 1995) to physical aggregation of whole marine organisms (Ackleh and Fitzpatrick, 1997) to aggregation of cells (Pawar et al., 2004; Bortz et al., 2008).

Here, we analyse two aggregation models in parallel: a minimal model that can be treated analytically, and a more biologically realistic numerical model that will be used to check the results and validate the assumptions made in the minimal model. Both models include three key processes (Fig. 1):

1. *Generation*: Aggregates of the smallest size class are generated at a constant rate a.
2. *Fusion*: Aggregates of size i and size j fuse at a constant rate $K(i,j)$. A biophysically reasonable kernel, and which will be used in the numerical model, is the Brownian kernel

$$K(i,j)=\frac{K}{4}\left(i^{1/3}+j^{1/3}\right)\left(i^{-1/3}+j^{-1/3}\right)$$

   first developed by Smoluchowski (1916). This kernel models the fusion of three-dimensional aggregates that move by Stokes diffusion and that fuse at an interaction radius in proportion to the sum of their own radii. In the minimal model, the Brownian kernel will be approximated with the constant kernel $K(i,j)=K$. Previous numerical studies have found this an accurate approximation (Axford, 1996; Krapivsky et al., 2010, and references therein). We also test this assumption by comparing results from the numerical and exact analytical results below.
3. *Continuous loss* (*minimal model*) *or division with random segregation* (*numerical model*): In the numerical model, at cell division each cell daughter is equally likely to inherit a given aggregate from the mother cell. To develop the minimal model,

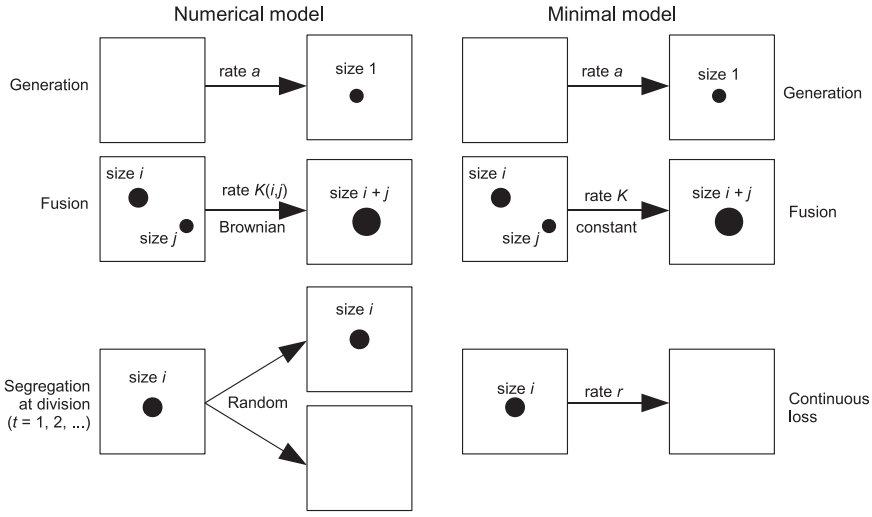

Fig. 1. The minimal and numerical models and their three processes. In the numerical model, aggregates of size 1 are generated at rate a, aggregates of sizes i and j fuse at rate $K(i,j)$ given by the Brownian kernel, and aggregates are randomly segregated between two daughters upon division. In the minimal model, aggregates of size 1 are generated at rate a, aggregates of sizes i and j fuse at constant rate $K(i,j)=K$, and aggregates are continually lost at rate $r=\ln 2$.