Mathematical Modeling of Spatial Propagation of Aβ oligomers

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Outline

Spatial progression in the brain

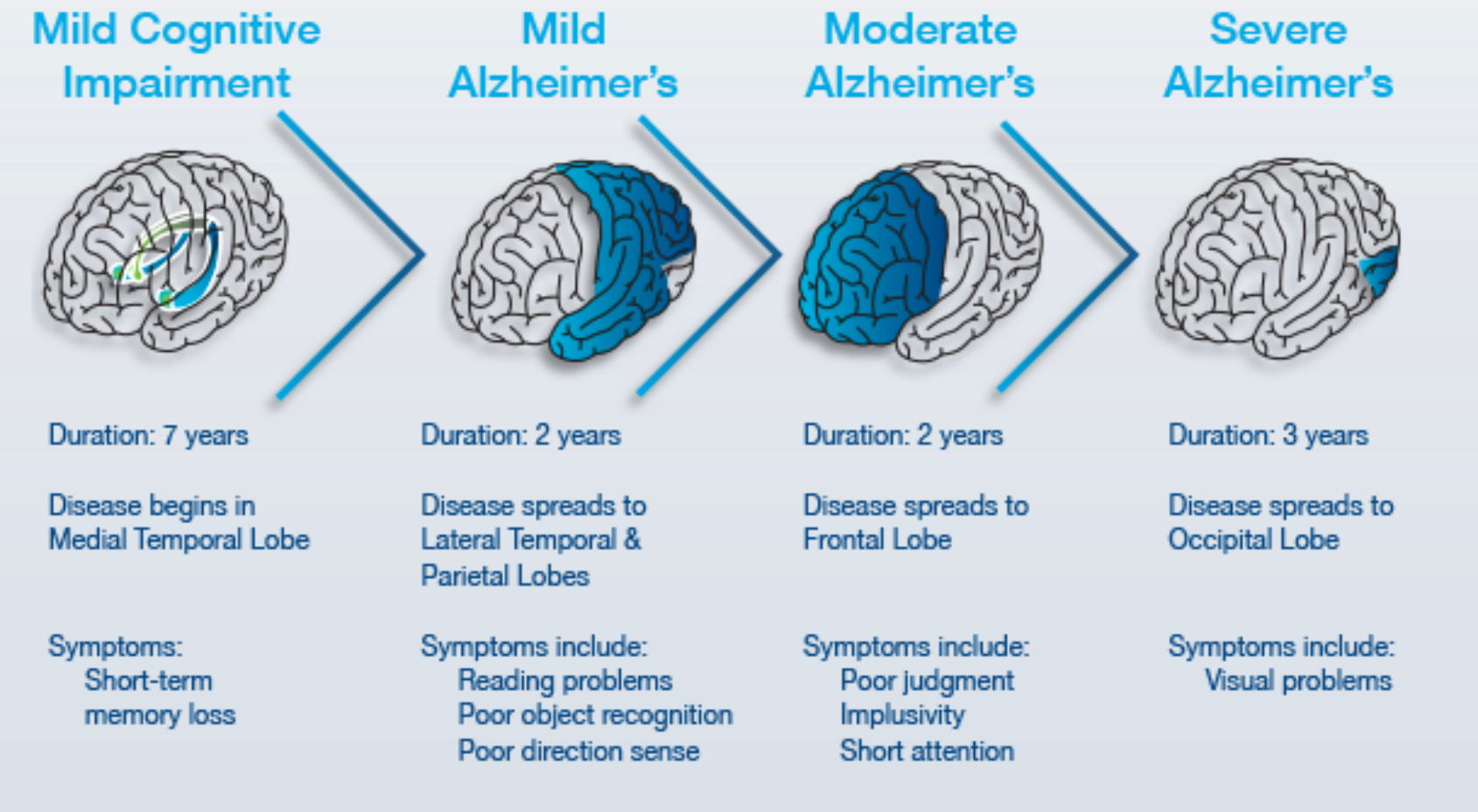


Figure: Figure from the "Medical Care Corporation"

The amyloid-beta protein

- Peptides of 36 to 43 amino acids from cleavage of APP (amyloid precursor protein)
- Aβ is produced by healthy neuronal cells throughout their life
- Its endogenous role is unclear
- Misfolded Aβ transforms normal Aβ and is prone to aggregation

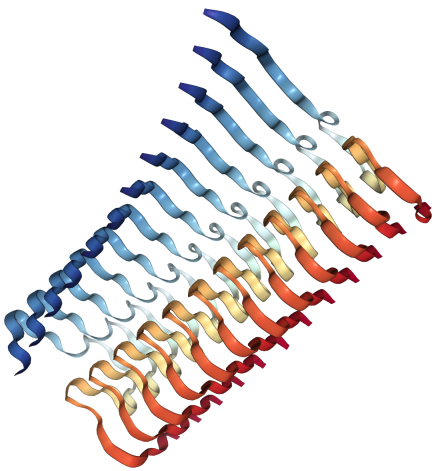
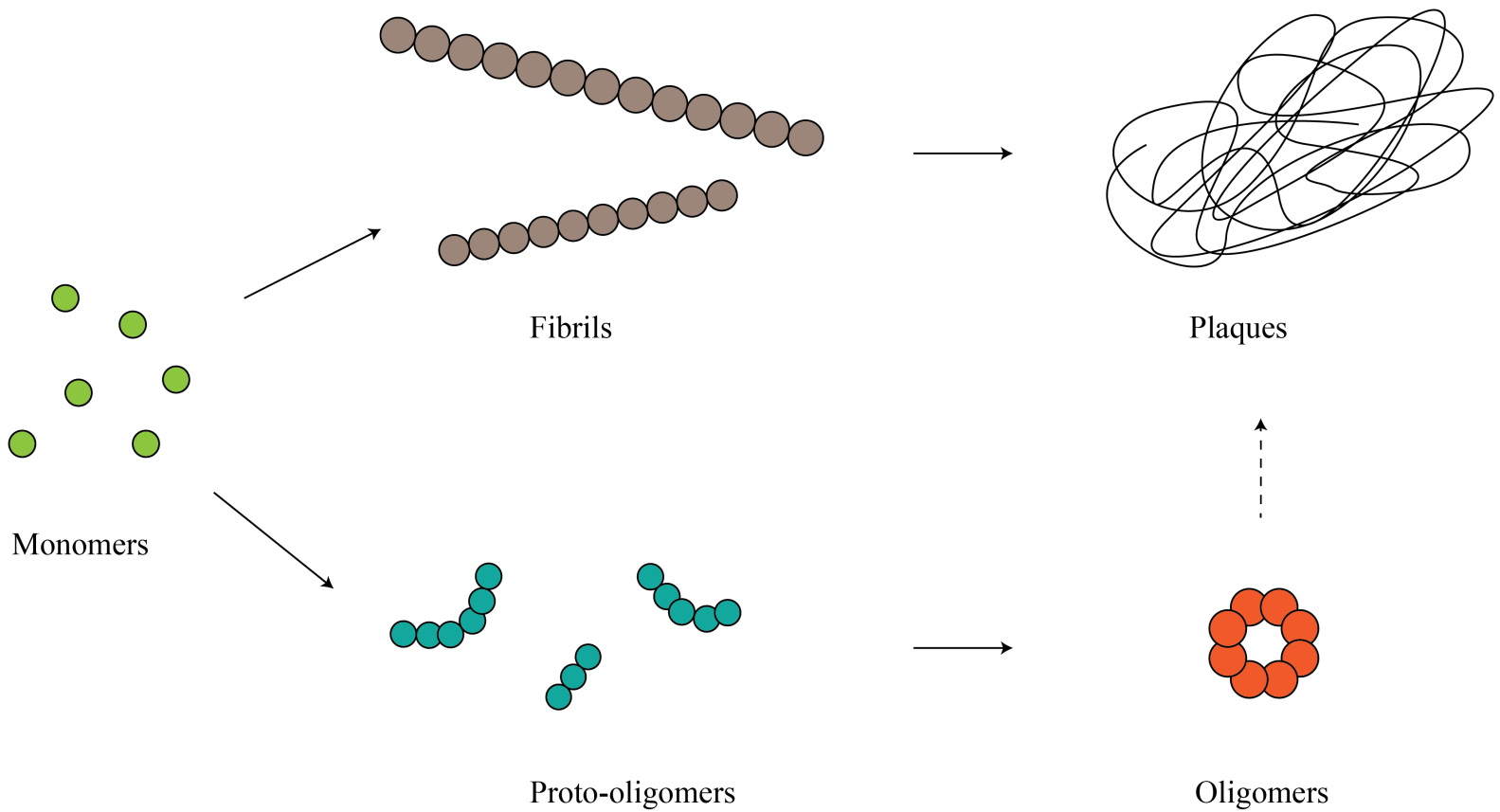


Figure: The Aβ protein

Aggregation pathways



The cascade hypothesis

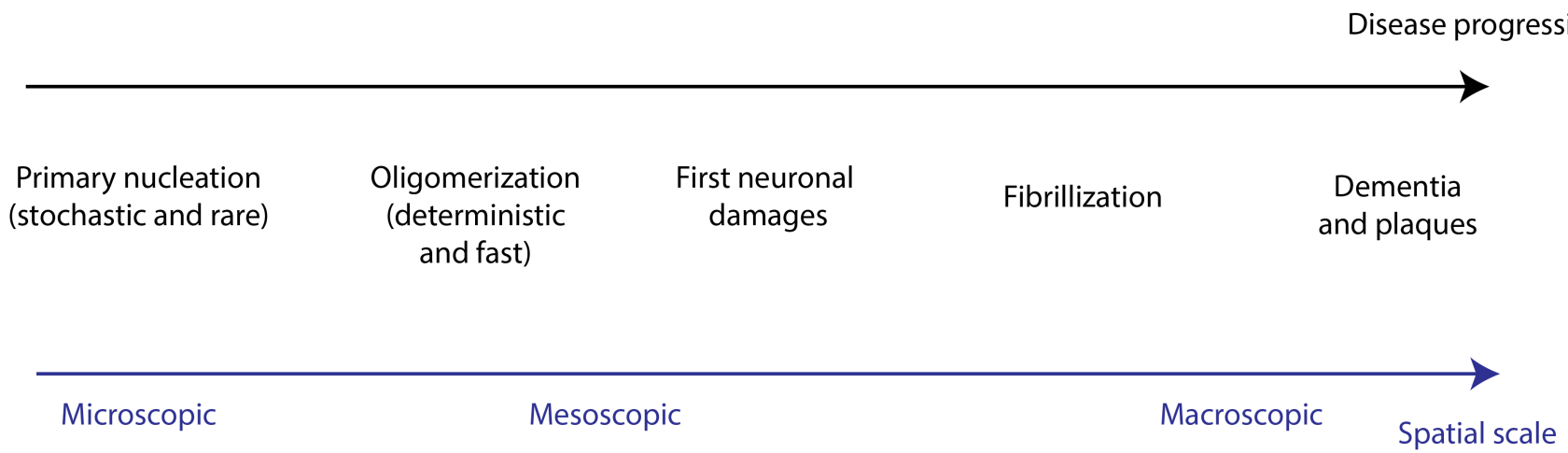


Figure: Schematic representation of the cascade hypothesis

Alzheimer's Disease: The Amyloid Cascade Hypothesis, Hardy, J. A. & Higgins, G. A., Science, 1992

Protein misfolding induced toxicity

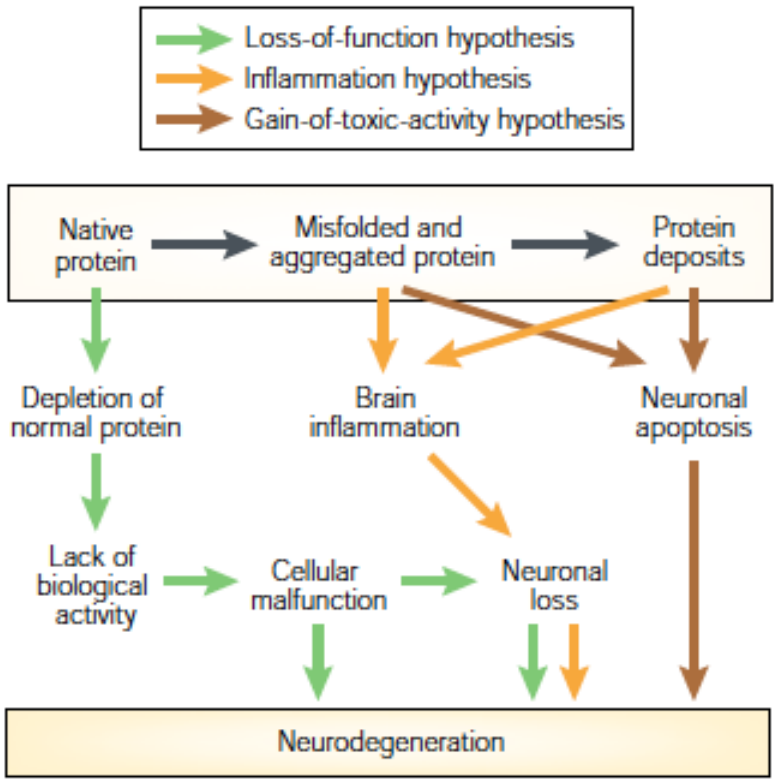


Figure: Figure from Soto, Science, 2003

Neurotoxicity depends on size

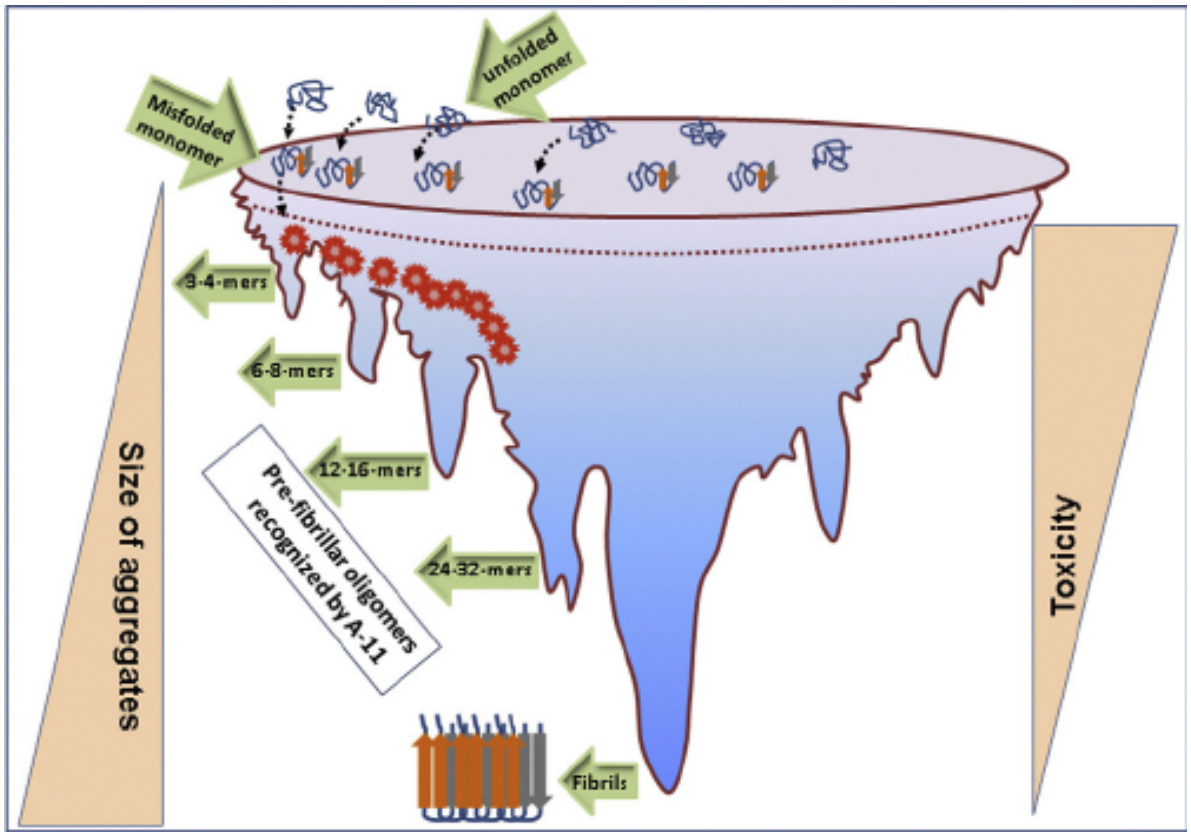


Figure: Figure from Sengupta et al. EBioMedicine, 2016

Progression in the brain

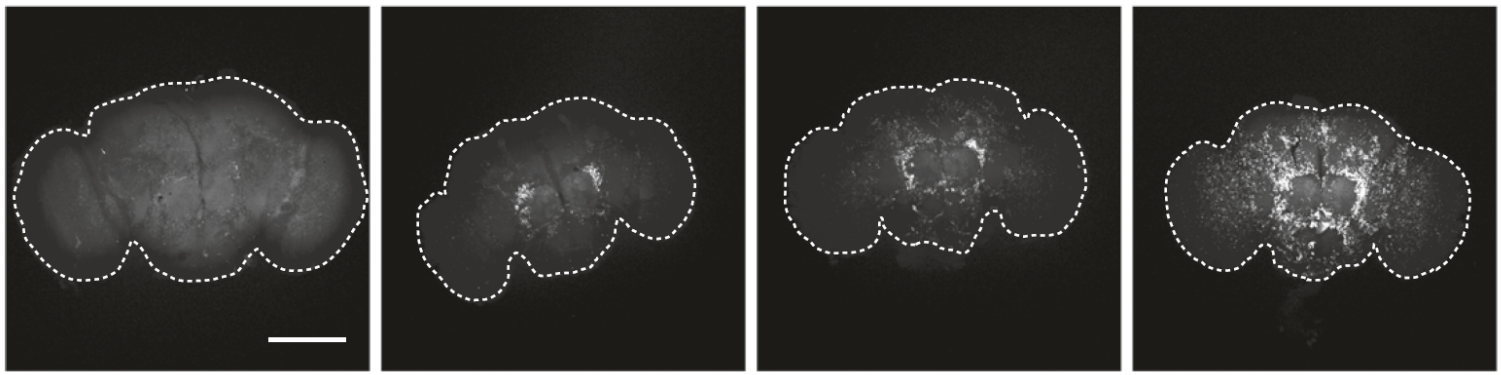


Figure: Figure from Sowade et al., Nature, 2017

- The spatial dynamics of Aβ proteins remain elusive
- Oligomers propagate from local seeds
- Microscopic $\rightarrow$ Stokes-Einstein Diffusion
- Macroscopic $\rightarrow$ other mechanisms (exosomes, astrocytes...)

Outline

A size-continuous model (non-spatial)

ALZHEIMER'S DISEASE AND PRION: AN *IN VITRO* MATHEMATICAL MODEL

IONEL S.CIUPERCA[1], MATTHIEU DUMONT[1,2], ABDELKADER LAKMECHE[3], PAULINE MAZZOCCO[1,2], LAURENT PUJO-MENJOUET[1,2], HUMAN REZAEI[4] AND LÉON M. TINE[1,2]

- Continuous in size
- No spatial propagation
- Fibrils, oligomers and plaques
- Interaction with Prion Protein (toxicity)

A spatial model

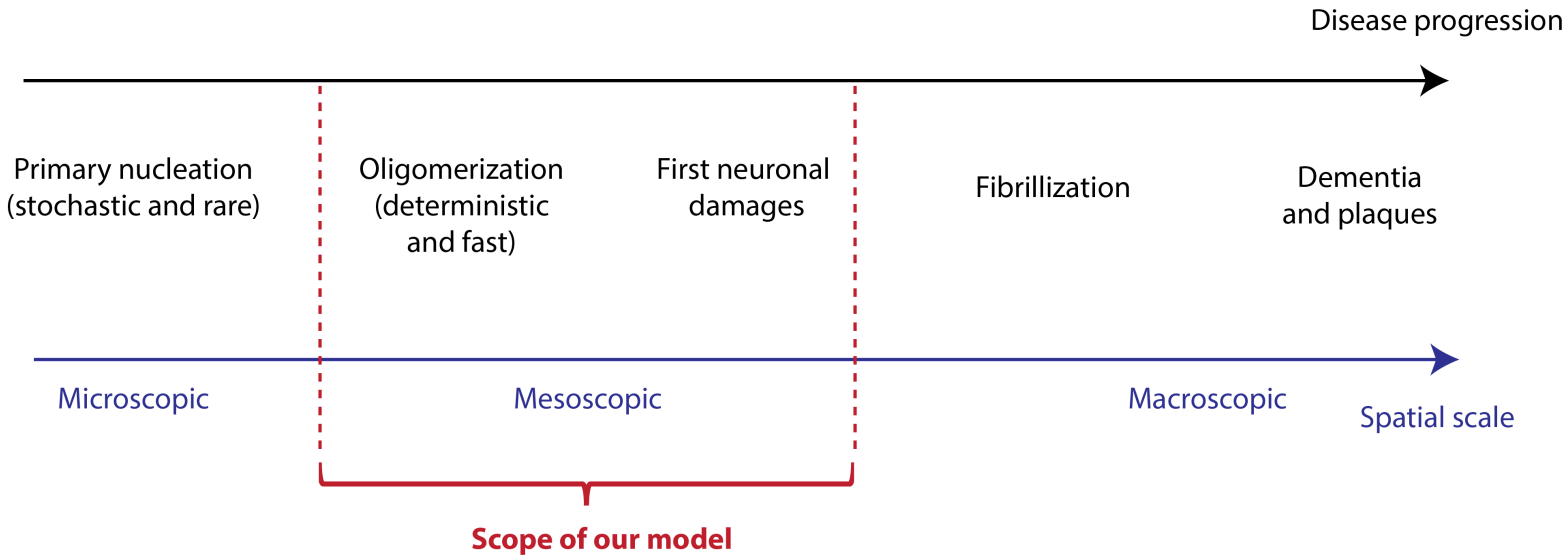
ALZHEIMER'S DISEASE: A MATHEMATICAL MODEL FOR ONSET AND PROGRESSION

MICHIEL BERTSCH, BRUNO FRANCHI, NORINA MARCELLO, MARIA CARLA TESI, AND ANDREA TOSIN

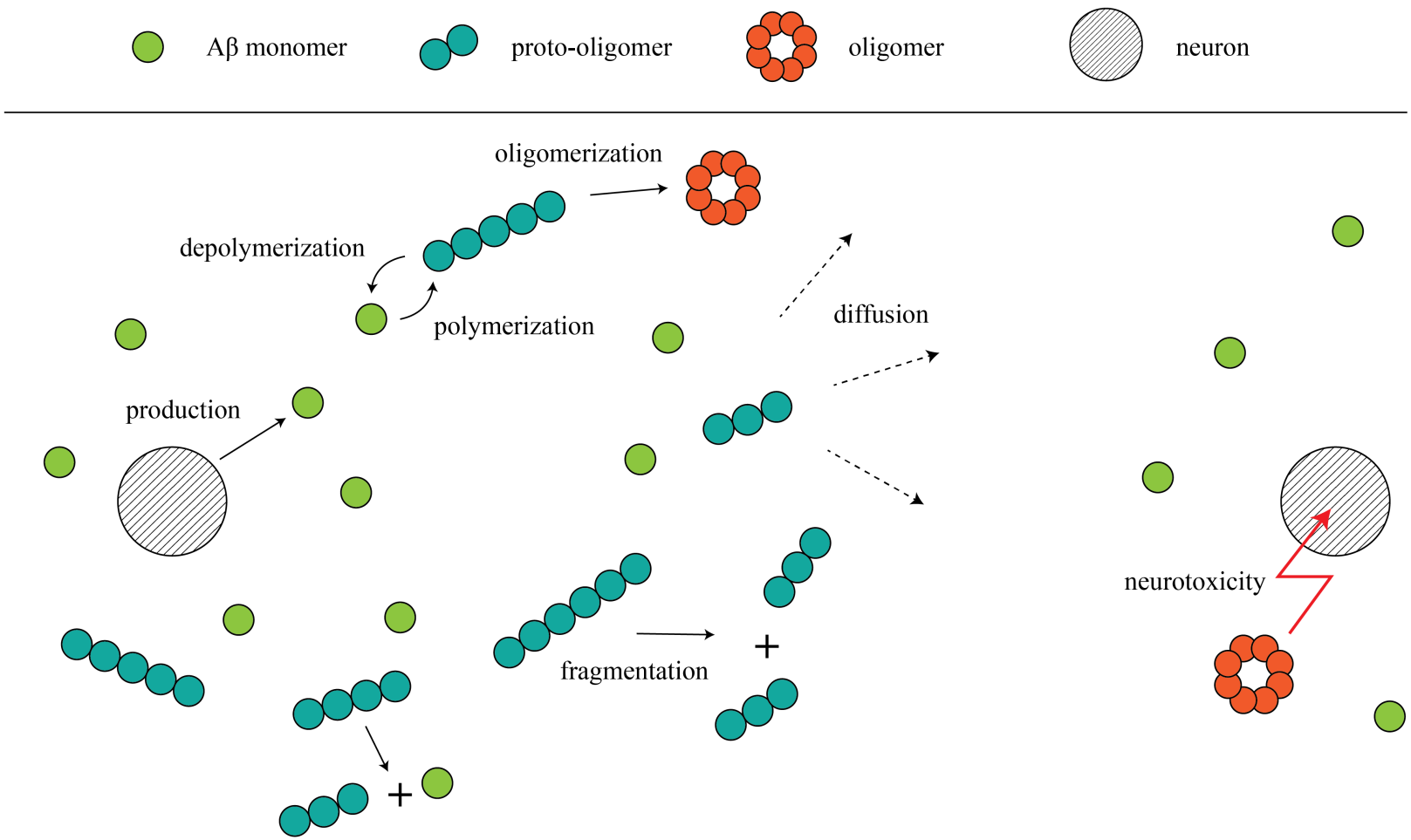
- Discrete in size
- Spatial propagation
- Fibril coalescence
- Mostly numerical, strong theoretical work but few biological justifications

Outline

Modeling scope



The biological model



Variables and notations

Local densities

- m: monomers
- μ_i: proto-oligomers of size i, for $i = 2 \dots i_0$ (i_0 for oligomers)

Processes

- Diffusion with coefficient D_i
- Polymerization with rate r_i
- Depolymerization with rate b
- Fragmentation with rate β_i
- Monomer production with rate λ_k (k for each neuron)
- Monomer degradation δ
- Absorption at the external boundary γ
- Neurotoxicity τ

Domain

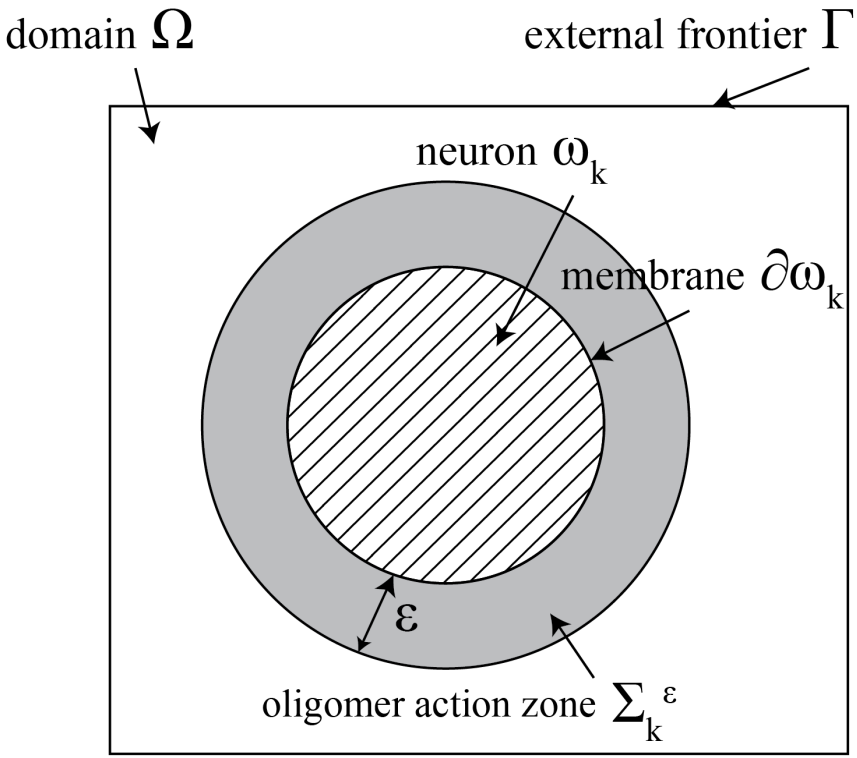


Figure: Domain definition and notations

The mathematical model

On Ω

$$\frac{\partial m}{\partial t} = D_1 \Delta m + \sum_{j=3}^{i_0-1} b\mu_j - \sum_{j=2}^{i_0-1} r_j \mu_j m + 2\beta \sum_{j=2}^{i_0-1} \mu_j - \delta m + \sum_{k=1}^{N} \lambda_k(t) \mathbb{1}_{\partial\omega_k}(x),$$

$$\frac{\partial \mu_i}{\partial t} = D_i \Delta \mu_i + b\mu_{i+1} - b\mu_i + r_{i-1}\mu_{i-1} m - r_i \mu_i m - \beta(i-1)\mu_i + 2\beta \sum_{j=i+1}^{i_0-1} \mu_j,$$

$$\frac{\partial \mu_{i_0}}{\partial t} = D_{i_0} \Delta \mu_{i_0} + r_{i_0-1}\mu_{i_0-1} m.$$

For $\xi = \mu_1 \dots \mu_{i_0}$

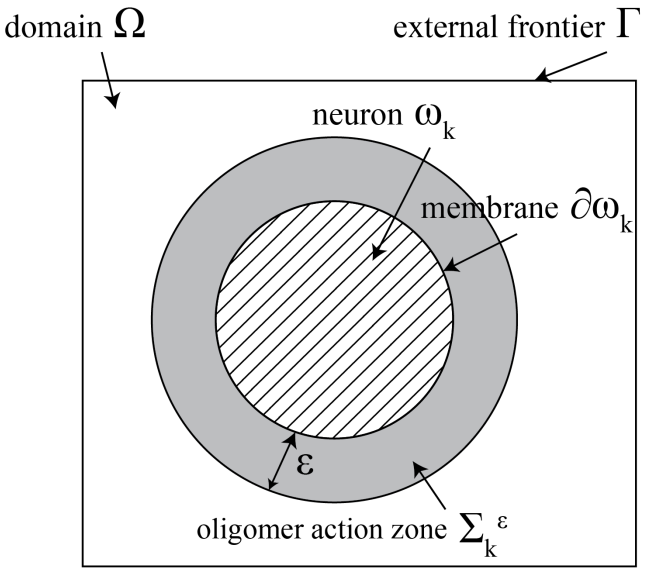
$$\nabla \xi \cdot \vec{n}|_\Gamma = -\gamma \xi \text{ and } \nabla \xi \cdot \vec{n}|_{\partial\omega_k} = 0.$$

Modeling neurotoxicity

Monomer production rate λ_k (of neuron k) verifies

$$\frac{d\lambda_k}{dt} = -\tau\lambda_k(t)\int_{\Sigma_k^\epsilon}\mu_{i_0}(x,t)dx,$$

$$\lambda_k(0) = \lambda_0.$$



Analytical results

Proposition

The system of partial differential equations has an unique solution in $E = L^2([0, T] \times \Omega) \cap L^\infty([0, T] \times \Omega)$.

Proposition

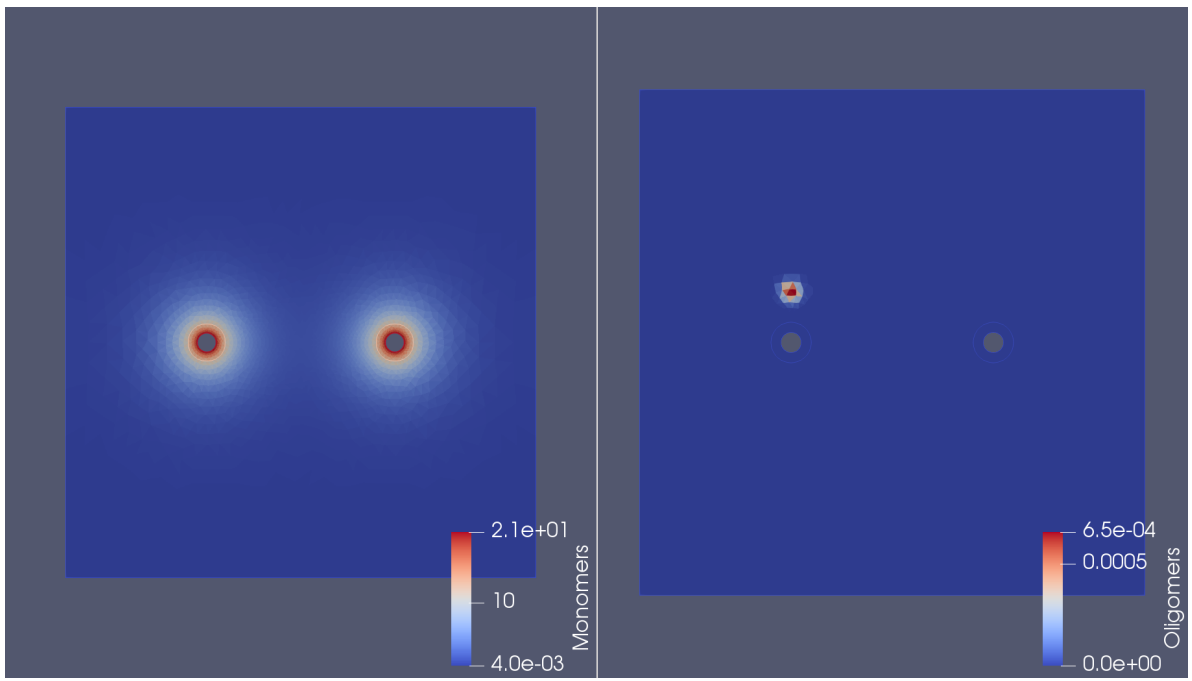
For non-negative initial conditions, the solution is non-negative at all times.

+ Boundedness under the right conditions.

Proofs to come in the proceedings.

Outline

- 2 (or 3) neurons
- Using Finite Elements Method with `Freefem++`
- Time integration with Euler scheme (implicit diffusion, explicit reaction)
- Initial condition: slightly perturbed healthy situation



Parameter choice

- Stokes-Einstein formula $D = \frac{k_b T}{6\pi\mu r_h} \approx 10^{-10} m^2.s^{-1}$
  We use $D \approx 10^{-14} m^2.s^{-1}$

Choices based on biological references and discussion with Human Rezaei (INRA, Jouy-en-Josas)

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- Spatial scale $L \approx 100\mu m$
- Concentration scale $C \approx 10^{-9} M(mol.L^{-1})$
- Order 1 reaction rates $\approx 10^{-4} - 10^{-3} s^{-1}$
- Polymerization rate $r \approx 10^{7} M^{-1} s^{-1}$
- Monomer production rate $\lambda \approx 10^{-13} M.s^{-1}$
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Critical parameters

Fragmentation rate $\beta \approx 10^{-5} - 10^{-3} s^{-1}$.
Toxicity efficiency $\tau \approx 10^{10} M^{-1}.s^{-1}$.

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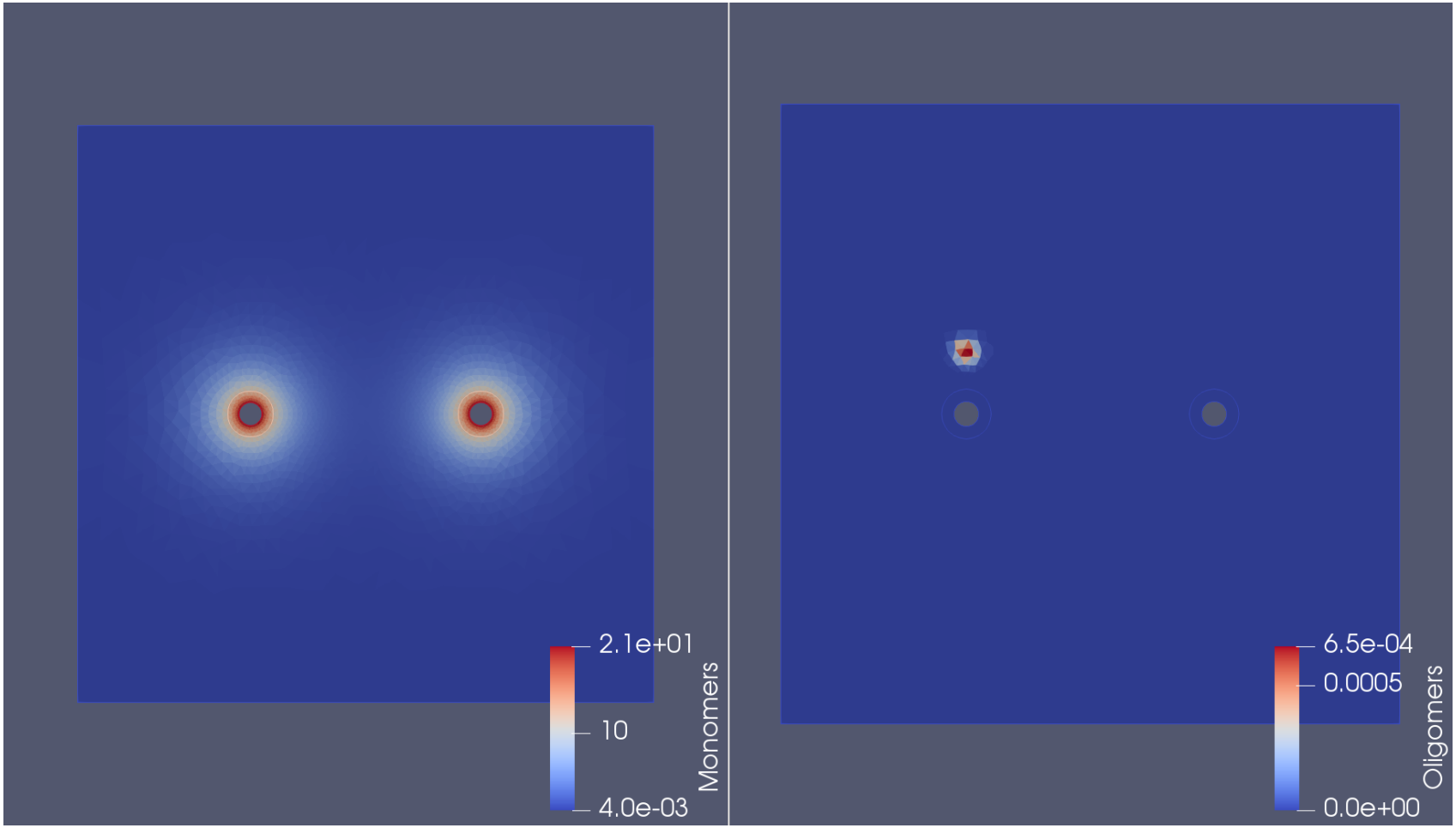
Fragmentation rate $\beta = 1.10^{-4} s^{-1}$



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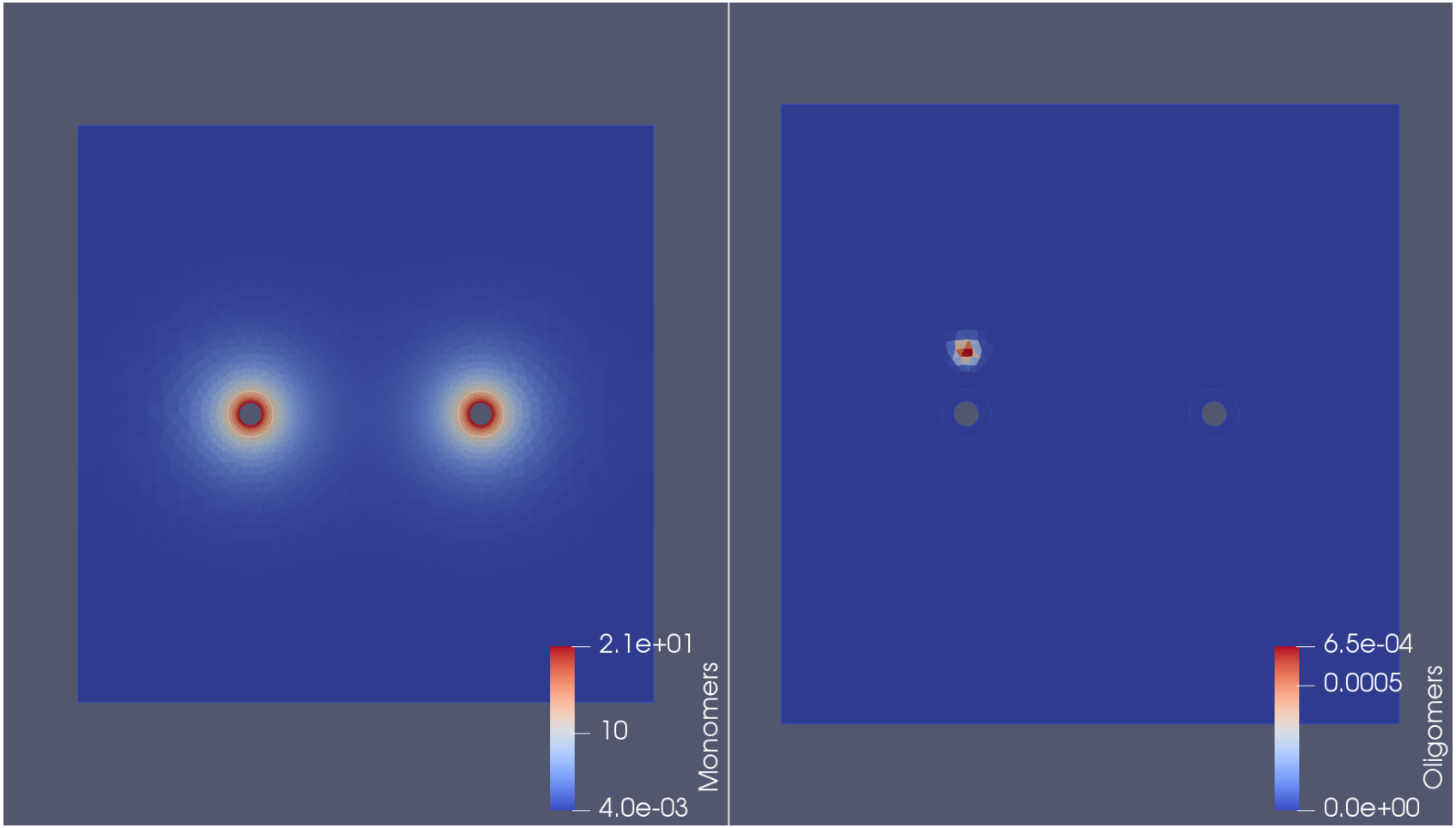
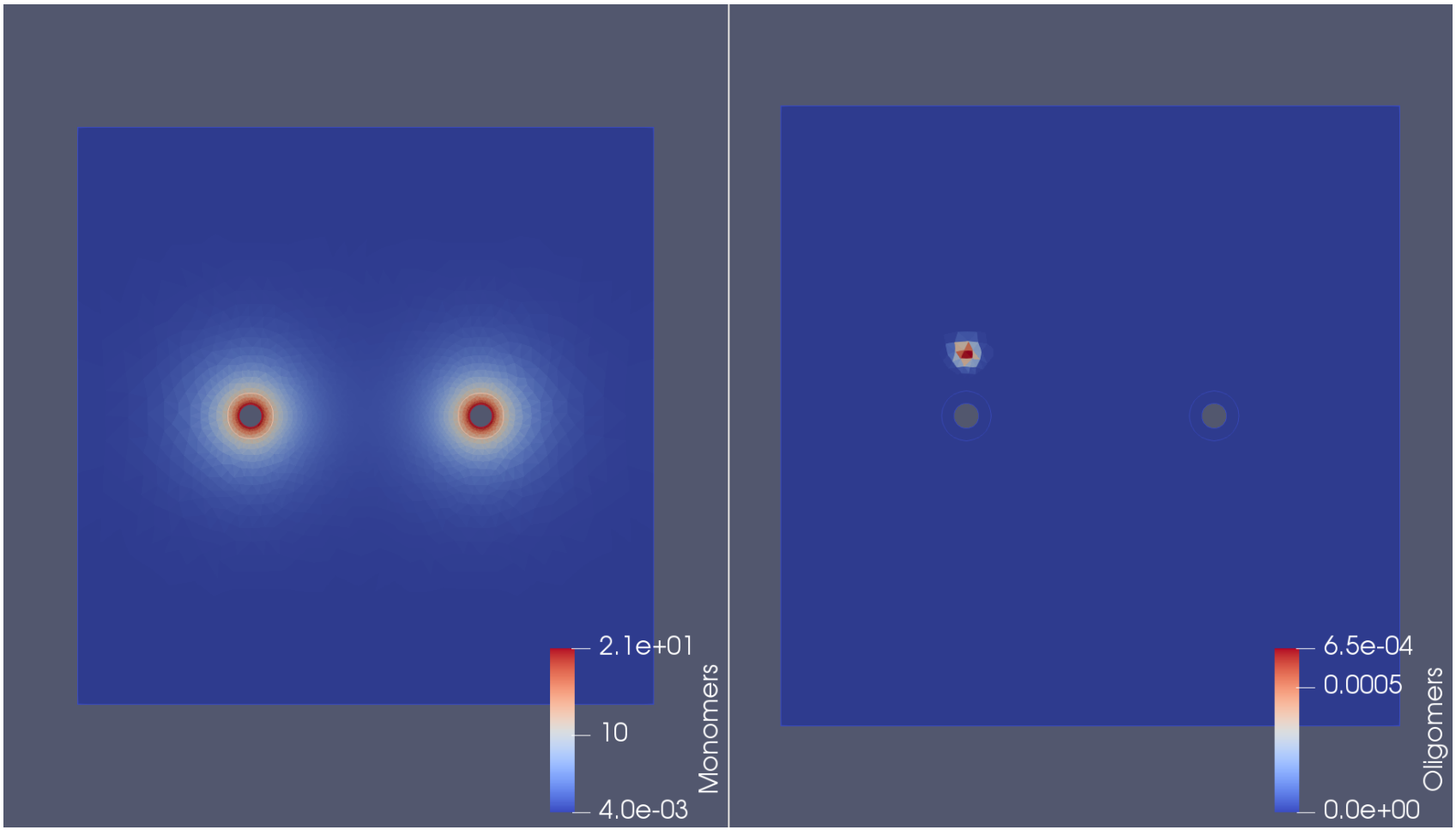
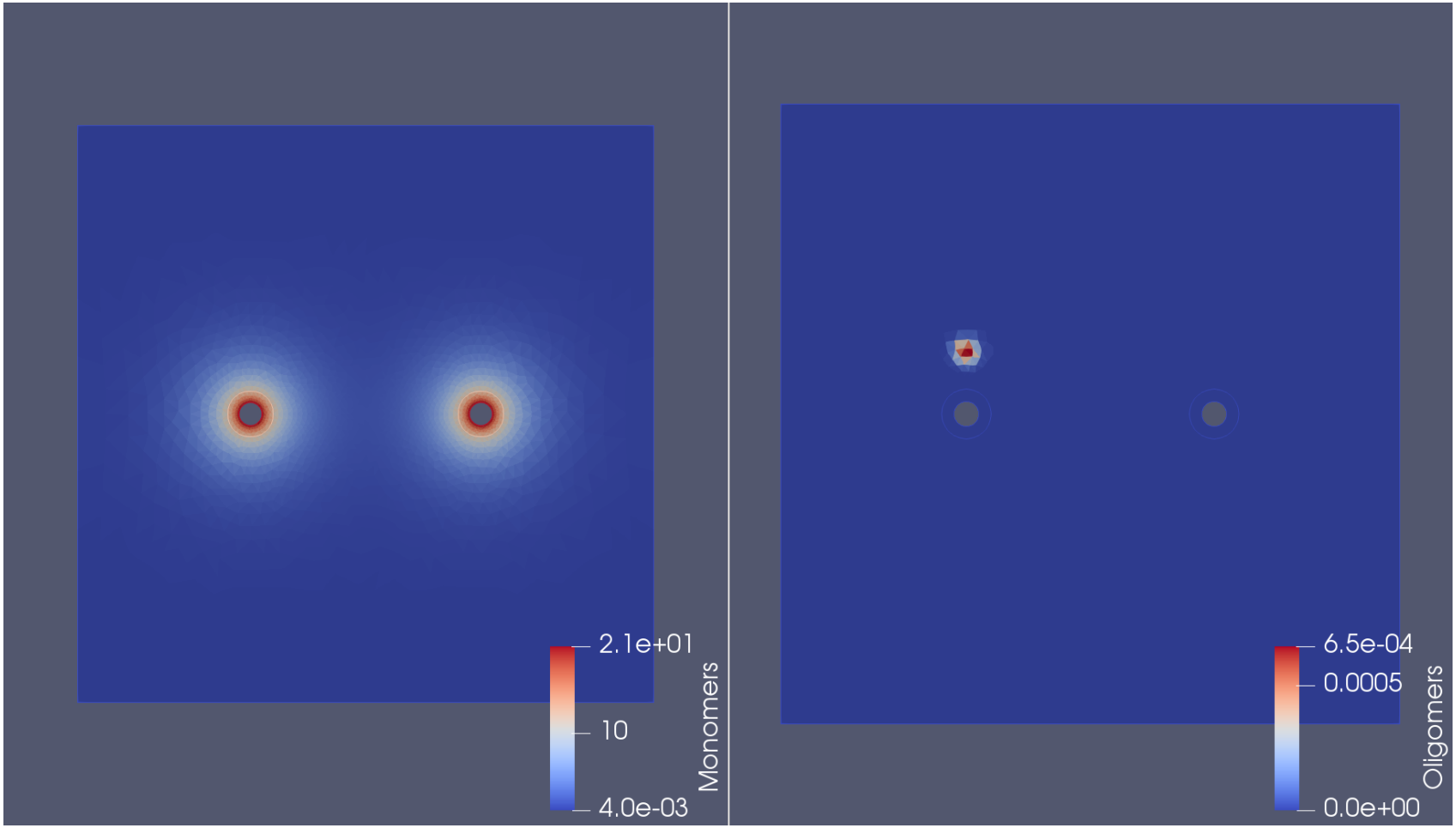


Fragmentation rate $\beta = 5.10^{-3}s^{-1}$



Just for fun ... with 3 neurons ($\beta = 1.10^{-4} s^{-1}$)



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- Optimize numerical simulation code
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Thank you for your attention !