

Additional file 1: Supplementary Model Equations, Tables, and Figures

Supplementary Model Equations

Model overview

We constructed a seven-variable coupled system of partial differential equations describing resting and activated macrophages and microglia, normal and damaged oligodendrocytes, pro-inflammatory and anti-inflammatory cytokines, and a neuroprotective astrocyte-like component. All state variables were treated as continuous functions of time t and spatial position (x, y) in a two-dimensional domain $\Omega \subset \mathbb{R}^2$. Diffusion terms were included only for variables assumed to spread spatially.

Model variables

- M_R : resting macrophages and microglia
- M_A : activated macrophages and microglia
- O_N : normal oligodendrocytes
- O_D : damaged oligodendrocytes
- C_1 : pro-inflammatory cytokines
- P : neuroprotective astrocyte-like component
- C_2 : anti-inflammatory cytokines

Governing equations

The governing equations are as follows:

$$\begin{aligned} \frac{\partial M_R}{\partial t} = & d_{M_R} \Delta M_R - k_{11} \frac{O_D^{m_1}}{k_{12}^{m_1} + O_D^{m_1}} M_R + k_{13} \frac{k_{14}^{m_2}}{k_{14}^{m_2} + O_D^{m_2}} M_A \\ & + k_{15} \{M_R^0 (O_N + O_D) - M_R\}, \end{aligned} \quad (S1)$$

$$\frac{\partial M_A}{\partial t} = d_{M_A} \Delta M_A + k_{11} \frac{O_D^{m_1}}{k_{12}^{m_1} + O_D^{m_1}} M_R - k_{13} \frac{k_{14}^{m_2}}{k_{14}^{m_2} + O_D^{m_2}} M_A + k_{16} O_D M_A, \quad (S2)$$

$$\frac{\partial O_D}{\partial t} = -k_{21} M_A O_D + k_{22} O_N \frac{C_1^4}{C_0^4 + C_1^4}, \quad (S3)$$

$$\frac{\partial O_N}{\partial t} = -k_{22} O_N \frac{C_1^4}{C_0^4 + C_1^4}, \quad (S4)$$

$$\frac{\partial C_1}{\partial t} = d_{C_1} \Delta C_1 + k_{31} \frac{P_0^{m_P}}{P_0^{m_P} + P^{m_P}} M_A - k_{32} C_1, \quad (S5)$$

$$\frac{\partial P}{\partial t} = k_{41} C_2 - k_{42} P, \quad (S6)$$

$$\frac{\partial C_2}{\partial t} = d_{C_2} \Delta C_2 + k_{51} M_A - k_{52} C_2. \quad (S7)$$

Description of model terms

In this model, M_R , M_A , C_1 , and C_2 were treated as spatially diffusing variables and therefore included diffusion terms. By contrast, O_N , O_D , and P were treated as local tissue-state variables and were assumed not to diffuse over the simulated timescale. Hill-type functions were used phenomenologically to represent saturating and threshold-like responses, whereas linear terms were used to represent local relaxation, production, and degradation. These functional forms were selected as simplified representations of the corresponding biological interactions rather than as direct descriptions of specific molecular mechanisms.

Resting macrophages and microglia (M_R)

The diffusion term in (S1) represents random motility. The two Hill terms describe O_D -dependent activation and deactivation: increasing O_D promotes activation and suppresses deactivation, thereby favoring the activated state in damaged regions [1, 2]. The final term relaxes M_R toward $M_R^0 (O_N + O_D)$, where M_R^0 is the baseline ratio of resting macrophages and microglia to the myelin content proxy.

Activated macrophages and microglia (M_A)

The diffusion term in (S2) represents the random motility of activated macrophages and microglia. In the baseline simulations, d_{M_A} was set to zero as a simplifying assumption, representing limited effective random redistribution of activated macrophages and microglia over the simulated timescale. This simplification was motivated by the context-dependent nature of microglial migration after injury [3]. The activation and deactivation terms mirror those in (S1). The term $k_{16}O_D M_A$ phenomenologically represents damage-associated local expansion and accumulation of activated macrophages and microglia, without specifying a particular mechanism of proliferation or recruitment.

Damaged oligodendrocytes (O_D)

The first term in (S3) represents the phagocytic removal of damaged oligodendrocytes and associated myelin material by activated macrophages and microglia [4–6]. The second term represents the conversion of O_N to O_D through C_1 -mediated injury, consistent with the cytotoxic effects of inflammatory mediators such as tumor necrosis factor- α [7, 8].

Normal oligodendrocytes (O_N)

Equation (S4) describes the loss of O_N through the same C_1 -mediated injury process that generates O_D . Direct phagocytic clearance of intact O_N was not included because intact myelin-forming tissue is relatively protected from phagocytosis by anti-phagocytic signaling, including the CD47–SIRP α pathway [5]. Because adult oligodendrocyte turnover is slow and substantial structural remyelination typically occurs over a period of weeks, no replenishment or remyelination term was included over the approximately one-week simulation period [9–11].

Pro-inflammatory cytokines (C_1)

The terms in (S5) represent diffusion, production by M_A under P -dependent suppression, and degradation. The P -dependent suppression is a coarse-grained representation of astrocyte-mediated regulation of the inflammatory activity of macrophages and microglia [8, 12, 13].

Neuroprotective astrocyte-like component (P)

Equation (S6) describes the induction of P by C_2 and its subsequent decay. P represents an aggregate astrocyte-mediated protective response rather than a single molecular species or astrocyte subtype. The formulation of P was motivated by IL-10- and TGF- β -associated astrocyte regulation and by anti-inflammatory astrocyte responses [13–15].

Anti-inflammatory cytokines (C_2)

The terms in (S7) represent diffusion, production by M_A , and degradation. Activated macrophages and microglia can produce anti-inflammatory mediators such as IL-10 [16, 17]. Because M_A represents a coarse-grained activated state, the model permits the production of both C_1 and C_2 and does not resolve distinct polarization states.

Supplementary Tables

Table S1: Initial conditions at $t = 0$.

Variable	Initial lesion seed ($r \leq 0.5$ mm)	Normal tissue ($r > 0.5$ mm)	Source
M_R	65 cells mm ⁻²	65 cells mm ⁻²	[18]
M_A	0 cells mm ⁻²	0 cells mm ⁻²	Assumed
O_D	360 cells mm ⁻²	0 cells mm ⁻²	Assumed
O_N	40 cells mm ⁻²	400 cells mm ⁻²	[19]
C_1	0 pg mm ⁻²	0 pg mm ⁻²	Assumed
P	0 cells mm ⁻²	0 cells mm ⁻²	Assumed
C_2	0 pg mm ⁻²	0 pg mm ⁻²	Assumed

Values were assigned as a radially symmetric, piecewise-constant (“top-hat”) seed with radius $r_0 = 0.5$ mm. Values labeled “Assumed” were chosen to be consistent with the model assumptions.

Table S2: Parameters of the mathematical model.

Parameter	Description	Value	Source
d_{M_R}	Random motility coefficient of resting macrophages and microglia	6.60×10^{-5} mm ² min ⁻¹	[20]
d_{M_A}	Random motility coefficient of activated macrophages and microglia	0 mm ² min ⁻¹	Estimated
d_{C_1}	Diffusion coefficient of pro-inflammatory cytokines	5.52×10^{-3} mm ² min ⁻¹	[21]
d_{C_2}	Diffusion coefficient of anti-inflammatory cytokines	5.52×10^{-3} mm ² min ⁻¹	[21]
k_{11}	Activation rate of resting macrophages and microglia	1.00 min ⁻¹	Estimated
k_{12}	Half-maximal activation constant for damaged oligodendrocyte-induced activation of resting macrophages and microglia	2.00×10^3 cells mm ⁻²	Estimated
k_{13}	Deactivation rate of activated macrophages and microglia	4.00×10^{-2} min ⁻¹	Estimated
k_{14}	Half-maximal constant for deactivation of activated macrophages and microglia	75.0 cells mm ⁻²	Estimated
k_{15}	Homeostatic relaxation rate of resting macrophages and microglia	1.00×10^{-1} min ⁻¹	Estimated
k_{16}	Damage-associated local amplification coefficient of activated macrophages and microglia	1.50×10^{-4} mm ² min ⁻¹ cells ⁻¹	Estimated
k_{21}	Phagocytic clearance rate of damaged oligodendrocytes by activated macrophages and microglia	3.00×10^{-5} mm ² min ⁻¹ cells ⁻¹	Estimated
k_{22}	Rate coefficient for oligodendrocyte injury induced by pro-inflammatory cytokines	3.00×10^{-3} min ⁻¹	Estimated
k_{31}	Production rate of pro-inflammatory cytokines by activated macrophages and microglia	1.00×10^{-2} pg min ⁻¹ cells ⁻¹	Estimated
k_{32}	Decay rate of pro-inflammatory cytokines	2.90×10^{-2} min ⁻¹	[22]
k_{41}	Induction rate of the neuroprotective astrocyte-like component by anti-inflammatory cytokines	1.50×10^{-4} cells min ⁻¹ pg ⁻¹	Estimated
k_{42}	Decay rate of the neuroprotective astrocyte-like component	1.75×10^{-5} min ⁻¹	[23]
k_{51}	Production rate of anti-inflammatory cytokines by activated macrophages and microglia	5.00×10^{-3} pg min ⁻¹ cells ⁻¹	Estimated
k_{52}	Decay rate of anti-inflammatory cytokines	2.60×10^{-3} min ⁻¹	[24]
M_R^0	Baseline ratio of resting macrophages and microglia to the myelin content proxy	1.625×10^{-1}	[18, 19]
C_0	Threshold for oligodendrocyte injury induced by pro-inflammatory cytokines	1.00×10^1 pg mm ⁻²	Estimated
P_0	Threshold for suppression of pro-inflammatory cytokine production by the neuroprotective astrocyte-like component	10.0 cells mm ⁻²	Estimated
m_1	Hill coefficient for activation of resting macrophages and microglia	16.0	Estimated
m_2	Hill coefficient for deactivation of activated macrophages and microglia	4.0	Estimated
m_P	Hill coefficient for suppression of pro-inflammatory cytokine production by the neuroprotective astrocyte-like component	20.0	Estimated

The table lists the parameter symbols, descriptions, baseline values, units where applicable, and sources used in the simulations. Dimensionless Hill exponents are indicated by m_1 , m_2 , and m_P . Values marked as “Estimated” were chosen to be consistent with our model assumptions and to reproduce the intended qualitative dynamics. All other values were informed by the cited references.

Table S3: Summary statistics of quantitative layer metrics in Baló’s concentric sclerosis pathology and the model.

Metric	Case 1	Case 2	Case 3	All cases	Model
Layer thickness (mm)	1.36 [1.03–1.70] (<i>n</i> = 36)	1.32 [1.11–1.91] (<i>n</i> = 26)	1.22 [1.01–1.79] (<i>n</i> = 45)	1.30 [1.02–1.78] (<i>n</i> = 107)	1.30 [1.30–1.35] (<i>n</i> = 36)
Adjacent-extrema intensity difference (a.u.)	0.17 [0.13–0.23] (<i>n</i> = 89)	0.14 [0.10–0.20] (<i>n</i> = 63)	0.35 [0.26–0.42] (<i>n</i> = 106)	0.23 [0.14–0.35] (<i>n</i> = 258)	0.08 [0.07–0.08] (<i>n</i> = 84)
Radial trend in layer thickness (mm/mm)	0.044 [-0.080–0.058] (<i>n</i> = 9)	0.084 [-0.013–0.116] (<i>n</i> = 6)	-0.047 [-0.256–0.046] (<i>n</i> = 11)	0.018 [-0.077–0.094] (<i>n</i> = 26)	-0.019 [-0.019–0.000] (<i>n</i> = 12)
Radial trend in maxima (a.u./mm)	0.023 [0.018–0.027] (<i>n</i> = 9)	0.030 [0.000–0.049] (<i>n</i> = 7)	0.014 [-0.010–0.032] (<i>n</i> = 11)	0.022 [0.000–0.030] (<i>n</i> = 27)	0.005 [0.005–0.006] (<i>n</i> = 12)
Radial trend in minima (a.u./mm)	-0.002 [-0.005–0.000] (<i>n</i> = 9)	0.008 [-0.002–0.033] (<i>n</i> = 7)	0.022 [0.007–0.027] (<i>n</i> = 11)	0.007 [-0.003–0.025] (<i>n</i> = 27)	0.002 [0.002–0.002] (<i>n</i> = 12)
Outer-minus-inner slope difference (a.u./mm)	0.052 [-0.031–0.203] (<i>n</i> = 44)	0.118 [0.039–0.310] (<i>n</i> = 28)	0.110 [-0.111–0.423] (<i>n</i> = 50)	0.092 [-0.041–0.288] (<i>n</i> = 122)	0.110 [0.101–0.126] (<i>n</i> = 36)

Data are presented as median [Q1–Q3], with *n* indicating the number of observations. The “All cases” column represents pooled layer- or extrema-level observations from Cases 1–3 and is provided as a descriptive summary rather than as a patient-level inferential analysis. The “Model” column represents values derived from the simulated Baló’s concentric sclerosis pattern. The outer-minus-inner slope difference was defined as |outer slope| – |inner slope|; positive values indicate a steeper outer slope. Values are rounded to two decimal places for layer thickness and adjacent-extrema intensity difference, and to three decimal places for radial-trend metrics and slope-difference values. Q1, first quartile; Q3, third quartile; a.u., arbitrary units.

Table S4: Holm-adjusted *p* values for one-sided Wilcoxon signed-rank tests against zero.

Metric	Case 1	Case 2	Case 3
Radial trend in layer thickness (mm/mm)	0.652 (<i>n</i> = 9)	0.234 (<i>n</i> = 6)	0.817 (<i>n</i> = 11)
Radial trend in maxima (a.u./mm)	0.029 (<i>n</i> = 9)	0.083 (<i>n</i> = 7)	0.083 (<i>n</i> = 11)
Radial trend in minima (a.u./mm)	0.898 (<i>n</i> = 9)	0.156 (<i>n</i> = 7)	0.037 (<i>n</i> = 11)
Outer-minus-inner slope difference (a.u./mm)	0.008 (<i>n</i> = 44)	0.001 (<i>n</i> = 28)	0.013 (<i>n</i> = 50)

For each metric, one-sided Wilcoxon signed-rank tests were performed separately in Cases 1–3 to assess whether the within-case observations showed a positive shift from zero. The three case-specific *p* values for each metric were adjusted using the Holm method. Here, *n* denotes the number of within-case observations included in each test. *p* values are reported to three decimal places. The tests were intended to characterize within-lesion spatial features rather than to provide population-level inference across patients. a.u., arbitrary units.

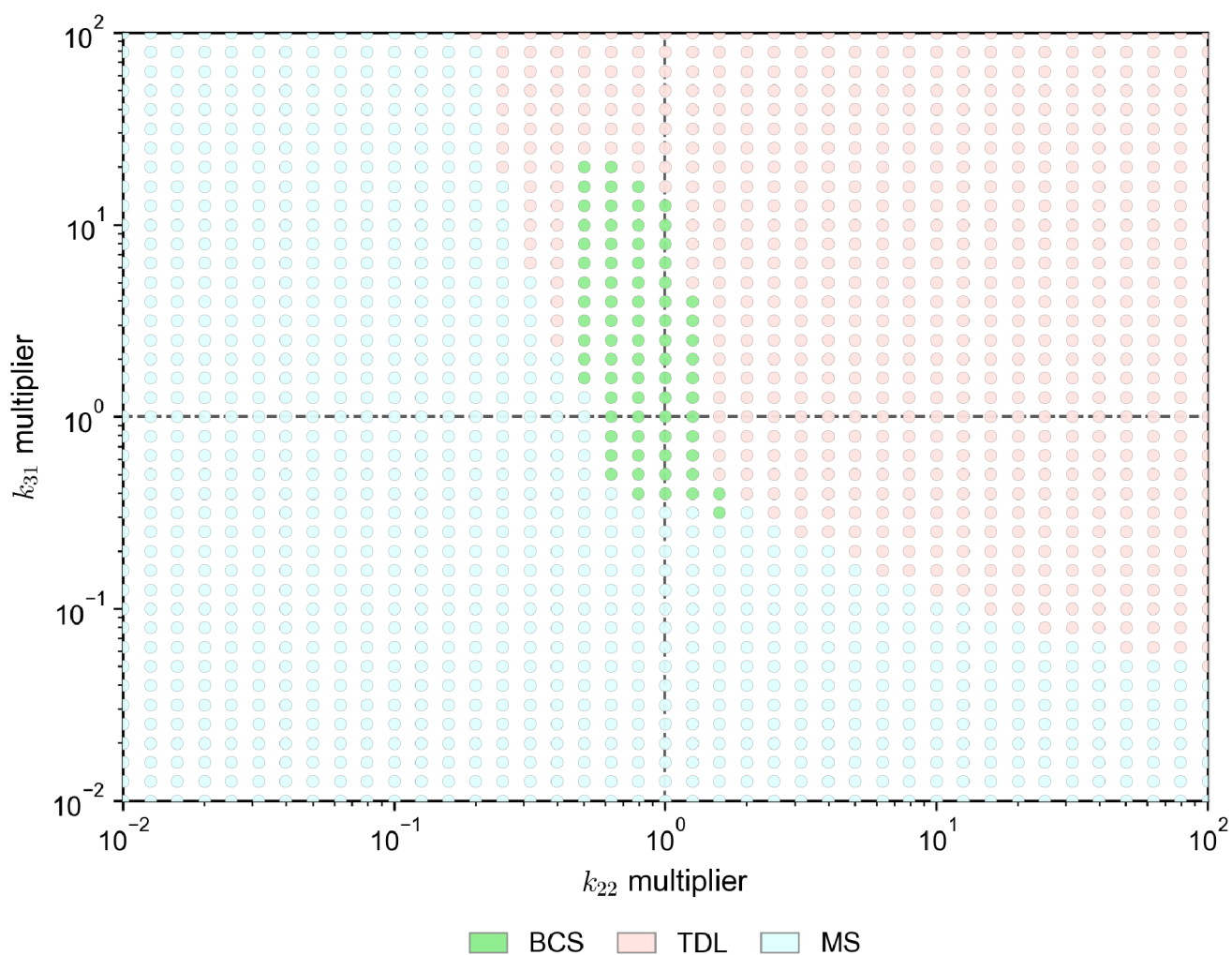


Figure S1: **Phase diagram from two-parameter sensitivity analysis of k_{22} and k_{31} .** Each circle represents one simulation performed with the indicated k_{22} and k_{31} multipliers relative to the baseline values. Colors indicate the resulting lesion pattern: Baló's concentric sclerosis (BCS) (green), tumefactive demyelinating lesion (TDL) (red), or multiple sclerosis (MS) (blue). The analysis showed a transition from the MS pattern at lower values of either parameter to the TDL pattern at higher values, with the BCS pattern emerging mainly in the intermediate transition region.

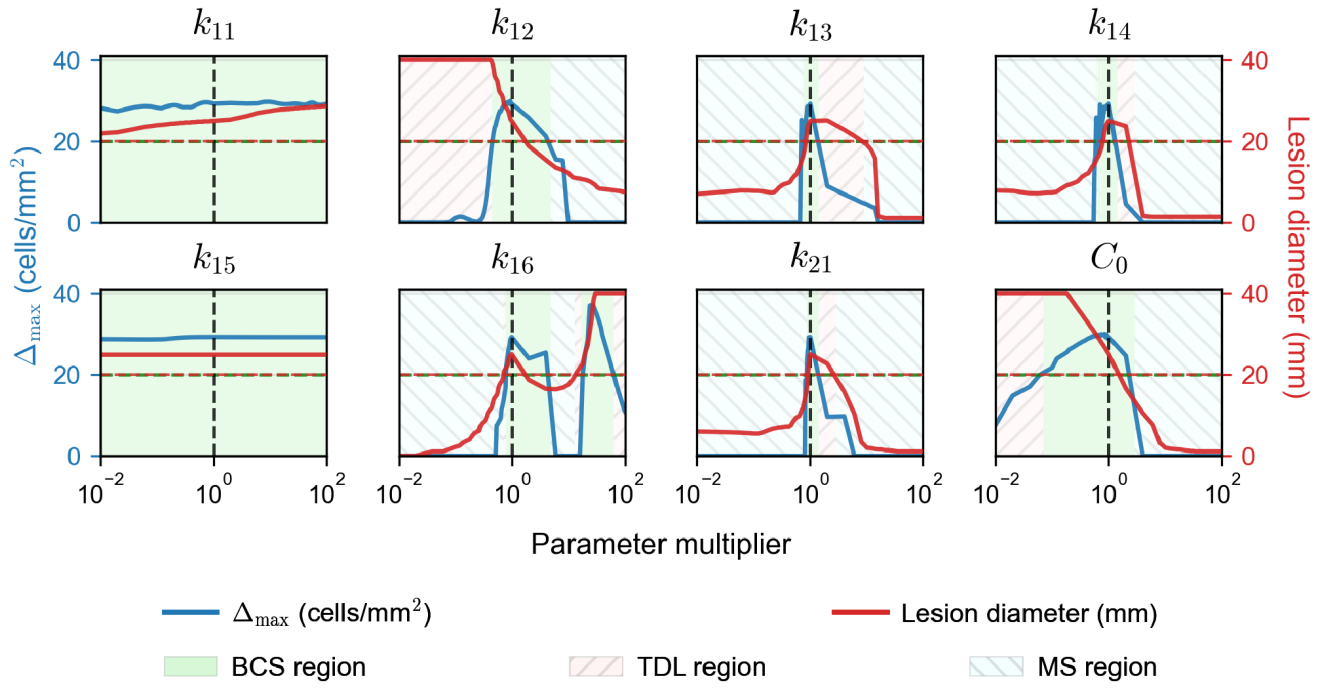


Figure S2: **Sensitivity analysis for additional parameters.** Each panel shows the effects of varying one parameter by multiplicative factors relative to its reference value on a log scale. The vertical black dashed line at 10^0 indicates the baseline value (Table S2). The blue curve represents the maximum interlayer difference, $\Delta_{\max}$ (cells/mm²), and the red curve represents lesion diameter (mm), calculated from the simulated lesion-front position. The horizontal dashed line indicates the classification thresholds of $\Delta_{\max} = 20$ cells/mm² on the left axis and lesion diameter = 20 mm on the right axis. Background shading indicates classification as the multiple sclerosis (MS), Baló's concentric sclerosis (BCS), or tumefactive demyelinating lesion (TDL) pattern.

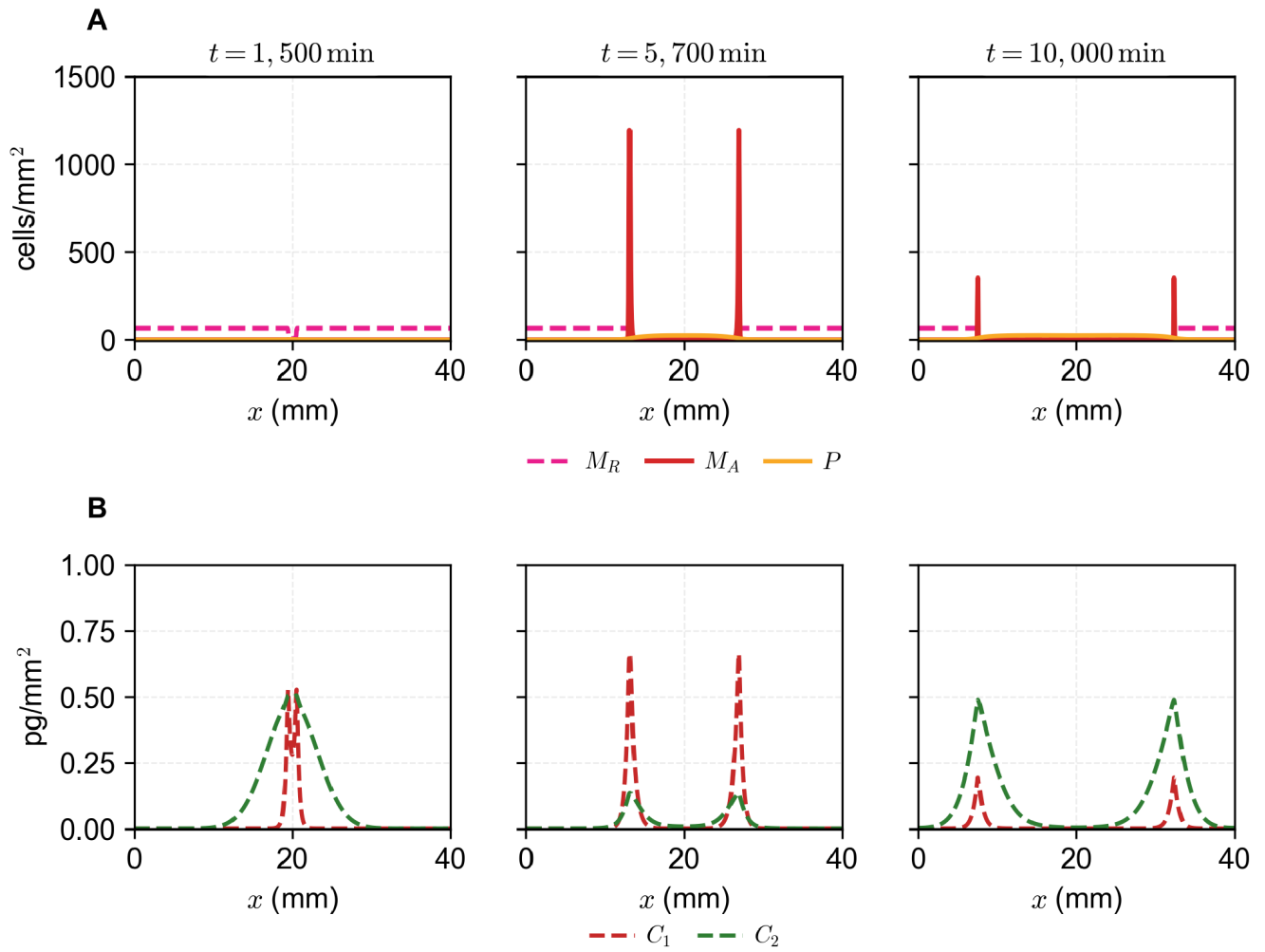


Figure S3: **One-dimensional profiles of cellular components and cytokines during Baló's concentric sclerosis pattern formation.** (A) Profiles of resting macrophages and microglia (M_R), activated macrophages and microglia (M_A), and the neuroprotective astrocyte-like component (P) along the horizontal transect through the lesion center ($y = 20 \text{ mm}$), shown at $t = 1,500, 5,700$, and $10,000 \text{ min}$. (B) Corresponding profiles of the pro-inflammatory cytokines (C_1) and anti-inflammatory cytokines (C_2) along the same transect. The x -axis indicates position along the transect in the simulation domain.

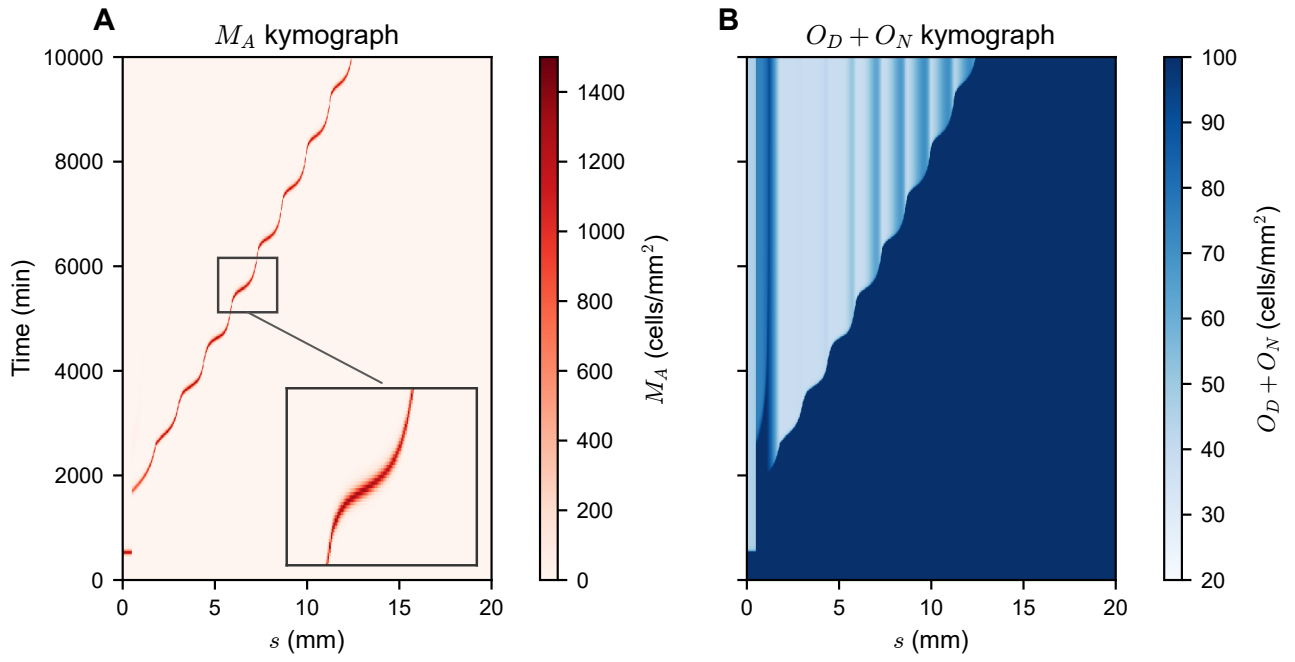


Figure S4: **Kymographs during Baló's concentric sclerosis pattern formation.** (A) Kymograph of activated macrophages and microglia (M_A), showing a narrow peak that propagates radially outward with oscillations in amplitude and propagation speed. (B) Kymograph of the myelin content proxy ($O_D + O_N$), showing lesion expansion and the formation of alternating zones of lower and higher myelin content proxy values behind the advancing front. The horizontal axis represents radial distance from the lesion center, the vertical axis represents time, and the color bars indicate cell density. For visualization of the lamellar structure, values above 100 cells/mm² were shown as saturated.

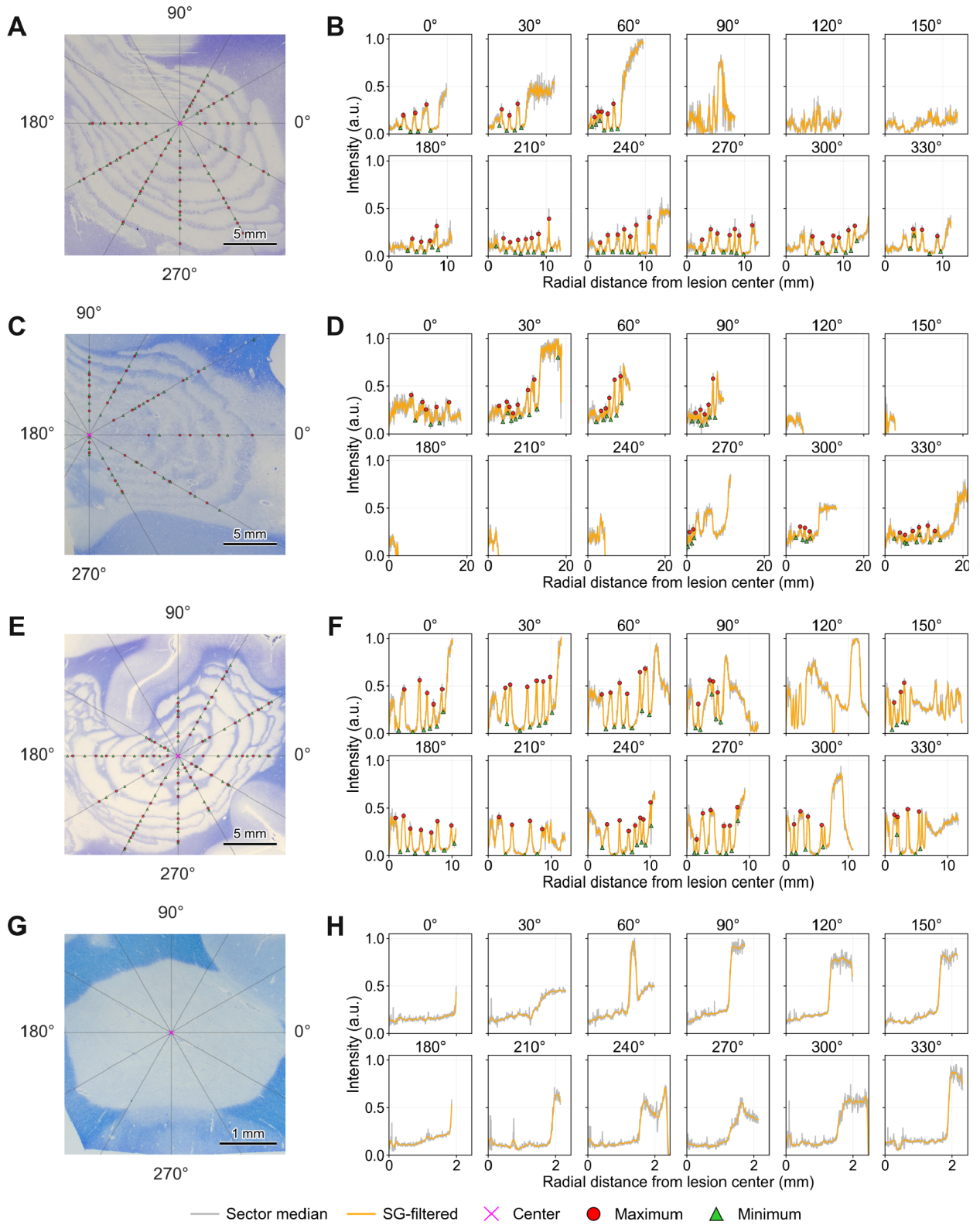


Figure S5: Radial profiles of myelin-related staining intensity in pathological Baló's concentric sclerosis and multiple sclerosis lesions. (A, C, E) Klüver-Barrera (KB)-stained sections from three Baló's concentric sclerosis (BCS) lesions showing the radial sampling scheme. The magenta cross indicates the lesion center, and gray lines indicate radial sampling directions at 30° intervals from 0° to 330°. Red circles and green triangles indicate local maxima and minima of KB staining intensity, respectively, detected along each radial profile. Scale bars: 5 mm. (B, D, F) Radial intensity profiles corresponding to (A, C, E), respectively. Gray traces show median profiles for each angular sector, and orange traces show Savitzky-Golay (SG)-filtered profiles. Red circles and green triangles denote the detected local maxima and minima, respectively. (G) KB-stained section from a multiple sclerosis (MS) lesion analyzed using the same radial-profile approach. Scale bar: 1 mm. (H) Radial intensity profile corresponding to (G). Intensity is expressed in arbitrary units (a.u.). Radial distance was measured from the lesion center for BCS lesions and from the sampling origin for the MS reference lesion.

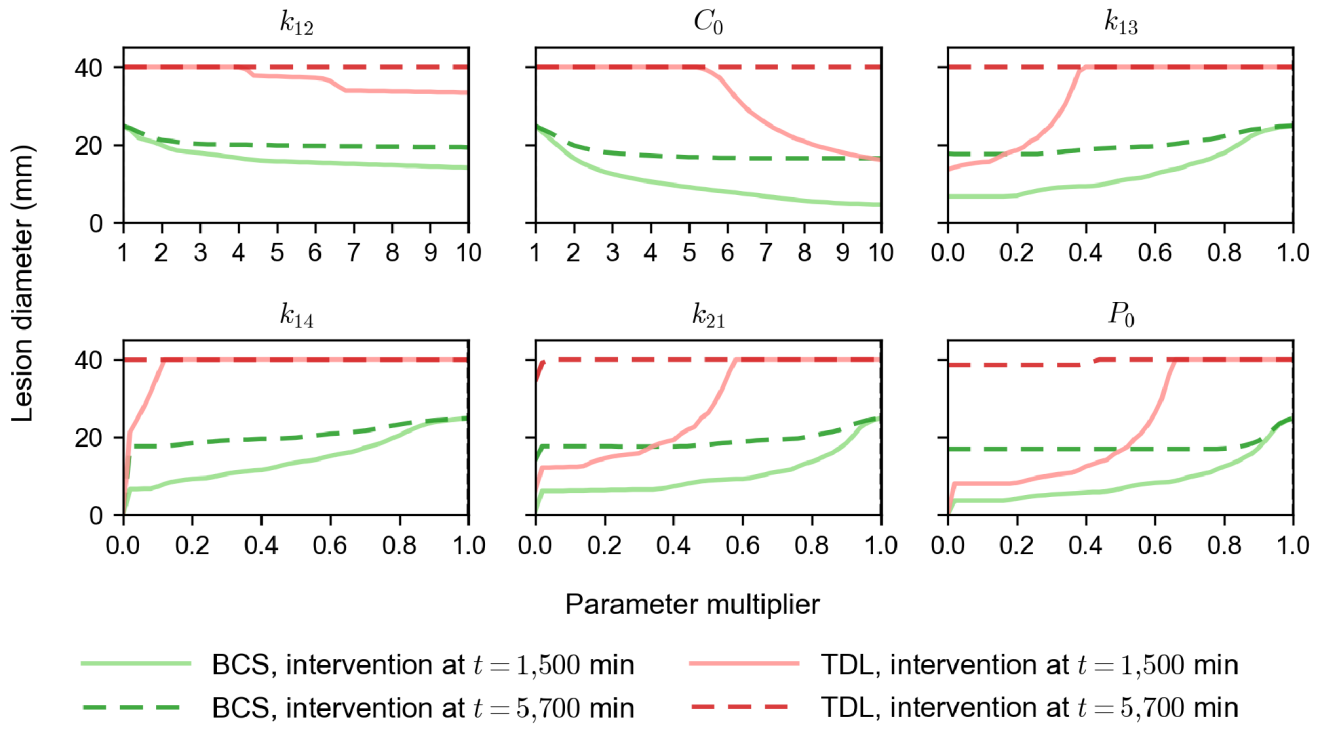


Figure S6: **Additional interventions alter lesion size in Baló's concentric sclerosis and tumefactive demyelinating lesion patterns.** For each parameter shown above the subplots (k_{12} , C_0 , k_{13} , k_{14} , k_{21} , and P_0), a post-onset intervention was simulated by changing a single parameter at $t = 1,500$ min (≈ 1 day) or $t = 5,700$ min (≈ 4 days), while keeping all other parameters fixed. The x -axis shows the parameter multiplier relative to the baseline value (Table S2), and the y -axis shows lesion diameter at $t = 10,000$ min. Green and red curves indicate simulations using the Baló's concentric sclerosis and tumefactive demyelinating lesion (TDL) parameter sets, respectively; solid and dashed curves indicate interventions initiated at $t_{\text{int}} = 1,500$ and $t_{\text{int}} = 5,700$ min, respectively. The TDL parameter set was generated by increasing k_{22} to $3.0 \times 10^{-2} \text{ min}^{-1}$. For k_{12} and C_0 , the parameter multiplier ranged from 1 to 10, whereas for k_{13} , k_{14} , k_{21} , and P_0 , it ranged from 0.01 to 1.

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