# SPARSE MODEL IDENTIFICATION AND PREDICTION OF MICROGLIAL CELLS DURING ISCHEMIC STROKE

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#### **SUMMARY**

Dynamics between key neuroinflammatory components, detrimental M1 and beneficial M2 microglial cells, are not fully understood post-ischemic stroke. To discover, model, and predict these dynamics, we use a method based on sparse identification of nonlinear dynamics (SINDy). The resulting datadriven dynamical system involves constant and linear terms but does not include nonlinear interactions between cells. Results show M2 microglial cell dominance of four days. Forward predictions capture potential long-term dynamics of microglial cells and suggest a persistent inflammatory response.

Key words: neuroinflammation, model identification, parameter estimation, experimental data

## **1 INTRODUCTION**

Microglial cells are key components in the neuroinflammatory response following ischemic stroke and can be both beneficial and detrimental to the outcome of stroke; however, the dynamics between these cells over time is not fully understood [1]. The purpose of this study is to contribute a data-driven model of microglial cells to aid in understanding their dynamics and to help predict their long-term behavior after stroke onset. To this aim, we use a method based on sparse identification of nonlinear dynamics (SINDy) to determine an ODE model for the microglial cell dynamics:

$$\dot{x}(t) = f(x(t)) \tag{1}$$

where the right-hand side function  $f : \mathbb{R}^2 \to \mathbb{R}^2$  is unknown. We identify the model using experimentally observed M1 and M2 microglial cell counts from middle cerebral artery occlusion (MCAO)induced stroke models in mice and a set of candidate basis functions. We use this model to help inform our biological understanding and make inferences about the microglial cell behavior over time.

### 2 METHODOLOGY

The following method, which we refer to as SINDy+DE, has three main steps. First, we use the SINDy algorithm to obtain a sparse model describing the change in M1 and M2 microglial cells over time directly from experimentally-observed time series data. Second, to quantify uncertainty, we use Generalized Sobol Sensitivity (GSS) analysis to rank the resulting SINDy model parameters according to their influence on a combined output of M1 and M2 microglial cells and estimate the three most sensitive parameters using Markov Chain Monte Carlo (MCMC)-based parameter estimation. Third, we utilize the point estimates from SINDy and random samples from the posterior distributions of the MCMC-estimated parameters to provide forecast predictions with forward propagation of uncertainty and analyze results through a biological lens.

**Data:** The microglial time series data used in this work is a compiled set of experimental data from mice models of permanent and transient MCAO. Data is presented as microglial cell counts from the penumbra area of the ischemic brain. We summarize the data in Figure 1; however, a more thorough



Figure 1: Left: Time series data for M1 and M2 microglial cells. Potential outlier data at Day 5 is highlighted in grey. Note that we omit this point during the SINDy step but include it for sensitivity analysis and parameter estimation. Right: Derivative approximation for use in the SINDy algorithm. We fit a fourth-order and second-order polynomial to the M1 and M2 microglial cell data, respectively, and analytically compute the derivatives.

description of the experimental studies and compilation of data is given in Amato and Arnold (2024) [2]. Within the SINDy step, we omit a potential outlier at Day 5 so that learned dynamics are not dependent on this point; however, within the robust parameter estimation step, we include the data at Day 5 so that we can utilize all available information.

**SINDy:** To determine  $f(\cdot)$ , we use the SINDy algorithm [3]. Briefly, we construct a candidate function library,  $\Theta(X)$ , a matrix where each column represents a potential candidate to be included in the functional form of  $f(\cdot)$ , and use Sequential Threshold Least Squares (STLS) to solve for  $\Xi$  in

$$\dot{X} = \Theta(X)\Xi\tag{2}$$

where  $\dot{X} = [\dot{M}1(t) \ \dot{M}2(t)]$  and  $\Xi$  is a matrix of coefficients multiplying the candidate functions. We use M1(t) and M2(t), the microglial cell time series data omitting Day 5, to construct  $\Theta(X)$  and include a constant term, linear terms, and quadratic nonlinearities to represent dynamics that could potentially occur between microglial cells:

$$\Theta(X) = \begin{bmatrix} 1 & M1(t_1) & M2(t_1) & M1(t_1)^2 & M2(t_1)^2 & M1(t_1)M2(t_1) \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & M1(t_{end}) & M2(t_{end}) & M1(t_{end})^2 & M2(t_{end})^2 & M1(t_{end})M2(t_{end}) \end{bmatrix}.$$
 (3)

We approximate derivative information for M1 and M2 microglial cells using a fourth-order LS polynomial fit to M1 microglial cell data and a second-order LS polynomial fit to M2 microglial cell data and analytically compute the derivative in each case (see Figure 1).

The STLS algorithm, an iterative parameter approximation technique, then alternates between finding a LS solution and discarding parameter values smaller than a prescribed threshold parameter,  $\lambda$ .

**GSS Analysis and MCMC-based Parameter Estimation:** Although the SINDy method yields point estimates for the parameters of the resulting ODE model, which can be used to propagate the model forward in time, we must use a more robust parameter estimation procedure to obtain a sense of uncertainty in our parameter estimates and forecast predictions. To this aim, we utilize GSS analysis to determine the most influential parameters in our model, taking into account both M1 and M2 microglial cell counts as outputs [4]. We then apply the Metropolis-Hastings (MH) algorithm to estimate the three most sensitive parameters using the MCMC toolbox for MATLAB [5].

Forecast Predictions with Forward Propagation of Uncertainty: The MCMC sampling procedure results in a posterior sample for each of the estimated model parameters. Therefore, there are different combinations of parameter values (in addition to the mean estimates) that can be used from the posterior to simulate the forward model. Additionally, since experimental data are only collected over a two week period, it is of interest to simulate predicted microglial cell counts beyond the four-teen days of observation. In an effort to quantify uncertainty in the model outputs and propagate this uncertainty forward in time with model predictions, we draw N = 1,000 random samples from



Figure 2: Resulting ODE model and simulated time series obtained from applying SINDy with threshold parameter  $\lambda = 0.01$  and the experimental M1 and M2 microglial cell data. Note that only linear terms are active within the resulting sparse model in Eqs. (4) and (5).

the estimated parameter posteriors and run the forward model using MATLAB's ode15s over the time interval [0, 50] days with each of these N parameter sets. After computing the forward model simulations, there are N predicted values that we use to calculate a mean and standard deviation at discretized time points every 0.1 time units over the interval [0, 50].

### **3 RESULTS AND CONCLUSIONS**

Figure 2 summarizes results of applying the SINDy method to the M1 and M2 microglial cell data shown in Figure 1 with a threshold value of  $\lambda = 0.01$ . Note that only the linear candidate functions, i.e., the constant coefficient, M1 microglial cells, and M2 microglial cells, are active in describing the M1 and M2 microglial cell derivatives over time. Biologically, this indicates that no interaction terms are needed to describe the microglial cell dynamics observed in this data set.

Figure 3 summarizes the results of applying GSS analysis to the ODE model in Eqs. (4) and (5), yielding the three most sensitive parameters:  $\theta_4$ ,  $\theta_5$ , and  $\theta_3$ .

Figure 4 shows the results of using MCMC to estimate the three most sensitive parameters as determined by GSS. The posterior distributions for all three estimated parameters are narrower than their priors, and the mean posterior estimate for  $\theta_4$  has shifted from its SINDy point estimate. The rightmost panel of Figure 4 displays the numerical solution to the model in (4)–(5) with  $\theta_3$ ,  $\theta_4$ , and  $\theta_5$  replaced by the mean of their respective posterior distributions.

Results emphasize an initial M2 cell dominance of about four days, followed by an eventual takeover of M1 cells. Forecast predictions, presented in Figure 5, reflect some



Figure 3: Results of GSS applied to the ODE model in (4)–(5). The ranking of parameter values from most to least sensitive is:  $\theta_4$ ,  $\theta_5$ ,  $\theta_3$ ,  $\theta_2$ ,  $\theta_1$ , and  $\theta_6$ .

trends shown in experimental data papers of ischemic stroke in various brain areas [6, 7, 8]. In particular, the forecast uncertainty bounds capture the M1 microglial cell count at Day 35 reported in [6], which is an MCAO ischemic stroke study in the penumbra; the M2 microglial cell count from this study is right outside the lower uncertainty bound. Additionally, model forecasts suggest significantly more M1 cells than M2 cells from fourteen days on and a persistent inflammatory response. Although experimental studies suggest that neuroinflammation may persist past fourteen days, the form of the lingering response is unknown. Our model suggests a decrease followed by an increase for both M1 and M2 cells. After Day 35, we may expect results to return to baseline values; however, our model



Figure 4: MCMC results for the ODE model in (4)–(5) when estimating the three most sensitive parameters. From left to right: histograms showing the prior (dashed line) and posterior (solid line) distributions of the three estimated parameters; scatter plots showing the correlation between pairs of parameters; and the resulting forward model computed using the posterior means from the estimated posterior distributions.



Figure 5: Model forecast predictions with forward propagation. Mean number of M1 (black) and M2 (red) microglial cells are plotted over time with corresponding uncertainty bounds. Black and red stars indicate the microglial cell time series data used within the MCMC algorithm, whereas the black and red solid dots at Day 35 are the number of M1 and M2 microglial cells, respectively, reported in [6].

appears to reach a steady state. Therefore, it is not clear that the current model captures biologically relevant dynamics over longer time intervals, and further measurements are needed for validation.

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