Supplementary Material (ESI) for Molecular BioSystems

Supplementary Methods: Practical limits for reverse engineering of dynamical systems: a statistical analysis of sensitivity and parameter inferability in systems biology models

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1 Bayesian Sensitivity Measures for Dynamical Systems

1.1 Sensitivity for Bayesian inference.

We are interested in assessing the inferability of model parameters in systems biology models, and here we adopt a Bayesian perspective, where we evaluate the information[1] contained in the posterior distribution about the true parameter value. This information can also be understood in terms of the sensitivity of the posterior in response to small changes in the parameter value. We thus have

$$\mathcal{S}(\theta) \triangleq \mathrm{E}\left[\left(\frac{\partial \ln \Pr(\theta|\mathcal{D})}{\partial \ln \theta} - \mathrm{E}\left[\frac{\partial \ln \Pr(\theta|\mathcal{D})}{\partial \ln \theta}\right]\right)^2\right], \quad \forall \theta \neq 0, \tag{1}$$

where $\mathrm{E}[\cdot]$ stands for the expectation over data; here and below we shall always assume that $\theta \neq 0$. As we show in in section 1.3, this equation is the Bayesian equivalent to the expected Fisher Information[2]. As a consequence, for a multi-dimensional parameter set, we can write the information or sensitivity matrix as[3],

$$\mathcal{S}_{i,j}(\theta) = \int \left(\frac{\partial \ln \Pr(\mathcal{D}|\theta)}{\partial \ln \theta_i}\right)^T \left(\frac{\partial \ln \Pr(\mathcal{D}|\theta)}{\partial \ln \theta_j}\right) \Pr(\mathcal{D}|\theta) d\mathcal{D} \tag{2}$$

for parameters θ_i and θ_j. Sensitivity defined thus is related to the confidence intervals obtained during parameter inferences.

1.2 Sensitivity for deterministic systems.

Here, we analyse the sensitivity of inferences from (potentially noisy) observations of deterministic systems at predefined time points. We assume that such a system evolves from a set of initial conditions (which we here assume to be known; incorporation of initial conditions into the inferential framework is straightforward). The observed data are thus described by

$$\delta_t = y(t,\theta) + \varepsilon_t,$$

where $y(t,\theta)$ is the output from the deterministic system, δ_t is the observation at time t, and $\varepsilon_t \sim \mathcal{N}(0,\sigma_t)$, is Gaussian noise characterized by σ_t is the variance of the experimental error at time t. Therefore, the likelihood of a single observation at a single time, t, obeys a Gaussian distribution. Using this likelihood and Eqn. (2), derived in detail below, we have for the sensitivity matrix,

$$\mathcal{S}_{i,j}(\theta) = \frac{1}{\sigma_t^2} \frac{\partial y(t,\theta)}{\partial \ln \theta_i} \frac{\partial y(t,\theta)}{\partial \ln \theta_j},$$

where θ_i and θ_j represent the i^{th} and j^{th} components of the parameter vector.

Generally we aim to observe the system at a set of time points, whence the overall sensitivity for the observations can be written as,

$$\mathcal{S}_{i,j}(\theta) = \sum_m \sum_t \frac{1}{\sigma_{t,m}^2} \frac{\partial y_m(t,\theta)}{\partial \ln \theta_i} \frac{\partial y_m(t,\theta)}{\partial \ln \theta_j},$$

where $y_m(t,\theta)$ represents the deterministic solution of the time-evolution of the species m, and $\sigma_{t,m}$ represents the standard deviation of the experimental error for the species m at time t.

The quantity,

$$\frac{\partial y(t,\theta)}{\partial \theta_i} = \frac{1}{\theta_i} \frac{\partial y(t,\theta)}{\partial \ln \theta_i}, \tag{3}$$

is referred to as a sensitivity coefficient for parameter θ_i at time t [3,4]. A range of sophisticated algorithms for calculating these sensitivity coefficients exist and for our sensitivity package, we prefer to use a combination of the ODE solver, CVODES [5], and the automatic differentiation library, CppAD [6].

1.3 Sensitivity and Information

The relationship between sensitivity and the Fisher's Information is evident upon careful inspection of the definition of sensitivity. When we elaborate on the expectation in Eqn. (1),

$$\mathrm{E}\left[\frac{\partial \ln \Pr(\theta|\delta)}{\partial \ln \theta}\right],$$

we obtain,

$$\begin{aligned}\int \frac{\partial \ln \Pr(\theta|\delta)}{\partial \ln \theta} \Pr(\delta|\theta) d\delta &= \int \frac{\partial \ln \Pr(\delta|\theta)}{\partial \ln \theta} \Pr(\delta|\theta) d\delta + \int \frac{\partial \ln \Pr(\theta)}{\partial \ln \theta} \Pr(\delta|\theta) d\delta \\ &= \frac{\partial \ln \Pr(\theta)}{\partial \ln \theta}.\end{aligned}$$

since the first integral equals zero. The sensitivity then becomes,

$$\begin{aligned}\mathcal{S}(\theta) &= \mathrm{E}\left[\left(\frac{\partial \ln \Pr(\theta|\delta)}{\partial \ln \theta} - \frac{\partial \ln \Pr(\theta)}{\partial \ln \theta}\right)^2\right] \\ &= \mathrm{E}\left[\left(\frac{\partial}{\partial \ln \theta} \ln \frac{\Pr(\theta|\delta)}{\Pr(\theta)}\right)^2\right] \\ &= \mathrm{E}\left[\left(\frac{\partial}{\partial \ln \theta} \ln \frac{\Pr(\delta|\theta)}{\Pr(\delta)}\right)^2\right] \\ &= \mathrm{E}\left[\left(\frac{\partial \ln \Pr(\delta|\theta)}{\partial \ln \theta}\right)^2\right] \\ &= \theta^2 I(\theta).\end{aligned}$$

where $I(\theta)$ is the standard form of the expected Fisher Information [2]. That means that in a Bayesian setting information is, i.e. the curvature around the maximum a-posteriori estimate, is given in terms of classical parameter sensitivity coefficients.

1.4 Deriving Sensitivity Matrix For Deterministic Systems

Here we derive the sensitivity matrix — in our setting as shown above, equivalent to the expected Fisher information — in detail. This is only for the sake of completeness as the derivation is standard[7,8]. Because we assume that the probability distribution is square integrable[9], the sensitivity matrix can be written in two forms; using first order partial derivatives as we present in Eqn. (2),

$$\mathcal{S}_{i,j}(\theta) = \int \frac{\partial \ln \Pr(\delta|\theta)}{\partial \ln \theta_i} \frac{\partial \ln \Pr(\delta|\theta)}{\partial \ln \theta_j} \Pr(\delta|\theta) d\delta, \tag{4}$$

or using second order partial derivatives,

$$\mathcal{S}_{i,j}(\theta) = -\int \frac{\partial^2 \ln \Pr(\delta|\theta)}{\partial \ln \theta_i \partial \ln \theta_j} \Pr(\delta|\theta) d\delta. \tag{5}$$

Following the assumptions in Supplementary Methods 1.2, we replace the likelihood in the sensitivity equations with a Gaussian

$$\Pr(\delta_t|\theta) = \frac{1}{\sqrt{2\pi}\sigma_t} \exp\left[-\frac{1}{2}\left[\frac{y(t,\theta)-\delta_t}{\sigma_t}\right]^2\right],$$

which can also we written as

$$\frac{\partial \ln \Pr(\delta_t|\theta)}{\partial \ln \theta} = -\left[y(t,\theta)-\delta_t\right] \frac{1}{\sigma_t^2} \frac{\partial y(t,\theta)}{\partial \ln \theta}.$$

Substituting this in the Eqn. (4) we arrive at

$$\mathcal{S}_{i,j}(\theta) = \int \frac{1}{\sigma_t^4} \frac{\partial y(t,\theta)}{\partial \ln \theta_i} \frac{\partial y(t,\theta)}{\partial \ln \theta_j} \left[y(t,\theta)-\delta_t\right]^2 \Pr(\delta|\theta) d\delta,$$

which simplifies further into

$$\mathcal{S}_{i,j}(\theta) = \frac{1}{\sigma_t^2} \frac{\partial y(t,\theta)}{\partial \ln \theta_i} \frac{\partial y(t,\theta)}{\partial \ln \theta_j},$$

because the variation in the data is Gaussian with standard deviation σ_t.

We can also arrive at the same solution using Eqn. (5). First we calculate the second order partial derivative of the likelihood

$$\frac{\partial^2 \ln \Pr(\delta_t|\theta)}{\partial \ln \theta_i \partial \ln \theta_j} = -\frac{1}{\sigma_t^2}\left[\frac{\partial y(t,\theta)}{\partial \ln \theta_i} \frac{\partial y(t,\theta)}{\partial \ln \theta_j} + \left[y(t,\theta)-\delta_t\right] \frac{\partial^2 y(t,\theta)}{\partial \ln \theta_i \partial \ln \theta_j}\right].$$

Then, using Eqn. (5), we write

$$\mathcal{S}_{i,j}(\theta) = \frac{1}{\sigma_t^2}\left[\frac{\partial y(t,\theta)}{\partial \ln \theta_i} \frac{\partial y(t,\theta)}{\partial \ln \theta_j} + \left[y(t,\theta)-\delta_t\right] \frac{\partial^2 y(t,\theta)}{\partial \ln \theta_i \partial \ln \theta_j}\right] \Pr(\delta|\theta) d\delta.$$

Since the expected value of the data are $y(t,\theta)$, we end up with the same solution as before,

$$\mathcal{S}_{i,j}(\theta) = \frac{1}{\sigma_t^2} \frac{\partial y(t,\theta)}{\partial \ln \theta_i} \frac{\partial y(t,\theta)}{\partial \ln \theta_j}.$$

The likelihood equations so far constituted of a single observation at a single time point. In the usual case where the data is a collection of observations, the likelihood can be written as

$$\Pr(\mathcal{D}|\theta) = \prod_m \prod_t \Pr(\delta_{t,m}|\theta)$$

where $\mathcal{D} = \{\delta_{t,m} | t \in \mathbb{R}^+, m \in \text{system components}\}$. When we obtain the logarithm and the second order partial derivative of this expression,

$$\frac{\partial^2 \ln \Pr(\mathcal{D}|\theta)}{\partial \ln \theta_i \partial \ln \theta_j} = -\sum_m \sum_t \frac{1}{\sigma^2_{t,m}} \left[\frac{\partial y_m(t,\theta)}{\partial \ln \theta_i} \frac{\partial y_m(t,\theta)}{\partial \ln \theta_j} + [y_m(t,\theta) - \mathcal{D}] \frac{\partial^2 y_m(t,\theta)}{\partial \ln \theta_i \partial \ln \theta_j} \right],$$

and we calculate the sensitivity as in Eqn. (5), since the expected value of the $\mathcal{D}$ are given by $y_m(t,\theta)$, we arrive at the multidimensional sensitivity matrix,

$$\mathcal{S}_{i,j}(\theta) = \sum_m \sum_t \frac{1}{\sigma^2_{t,m}} \frac{\partial y_m(t,\theta)}{\partial \ln \theta_i} \frac{\partial y_m(t,\theta)}{\partial \ln \theta_j}, \forall \theta \neq 0.$$

This finally links up sensitivity coefficients and the expected Fisher information (or sensitivity matrix).

2 The Smallest System with a Hopf Bifurcation

The set of ODEs for the chemical oscillating system is given by the following set of equations[10,11]:

$$\begin{aligned} \dot{x_1} &= A_0 k_1 x_1 - k_4 x_1 - k_2 x_1 x_2 \\ \dot{x_2} &= -k_3 x_2 + k_5 x_3 \\ \dot{x_3} &= k_4 x_1 - k_5 x_3 \end{aligned}$$

The system has three dimensions with six parameters in total including the species A_0 whose concentration is fixed. There are two fixed points, which obey the relationships,

$$p_1 = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}, \quad p_2 = \begin{pmatrix} \frac{k_3}{k_4} \frac{A_0 k_1 - k_4}{k_2} \\ \frac{k_3}{k_5} \frac{A_0 k_1 - k_4}{k_2} \\ \frac{A_0 k_1 - k_4}{k_2} \end{pmatrix}$$

By linearising the ODEs at these fixed points, using the initial point $(1,1,1)^{\mathrm{T}}$, and the parameters, $k_1 = 1$, $k_2 = 0.01$, $k_3 = 1$, $k_4 = 0.5$, $k_5 = 1$, we observe that the system settles on the attractor p_1 for $A_0 < 0.5$, and then on p_2 for $A_0 > 0.5$. In Figure 1, we show the three eigenvalues of the linearised system for the corresponding attractors with respect to the parameter A_0.

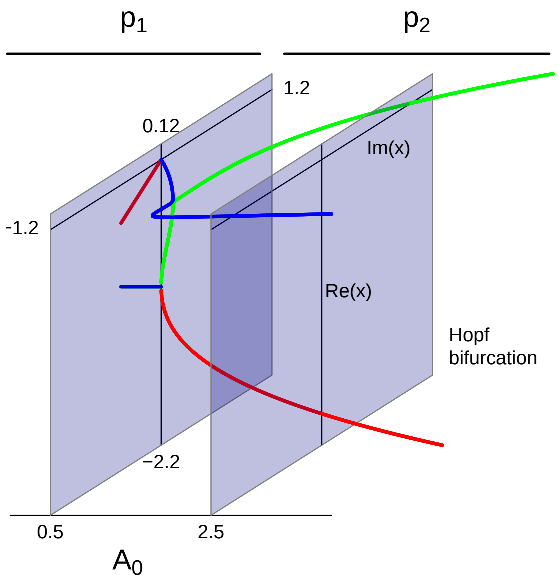

Figure 1 The three distinct global dynamical behaviours for the chemical oscillating system.The plot shows the stability of the system for the attractors p_1 for $A_0 < 0.5$, and for p_2 for $A_0 > 0.5$. The system exhibits a stable node for the attractor p_1. At $A_0 = 2.5$ the systems exhibits a Hopf bifurcation and the attractor p_2 is therefore a stable limit cycle. The three eigenvalues of the system are coloured in red, green, and blue.

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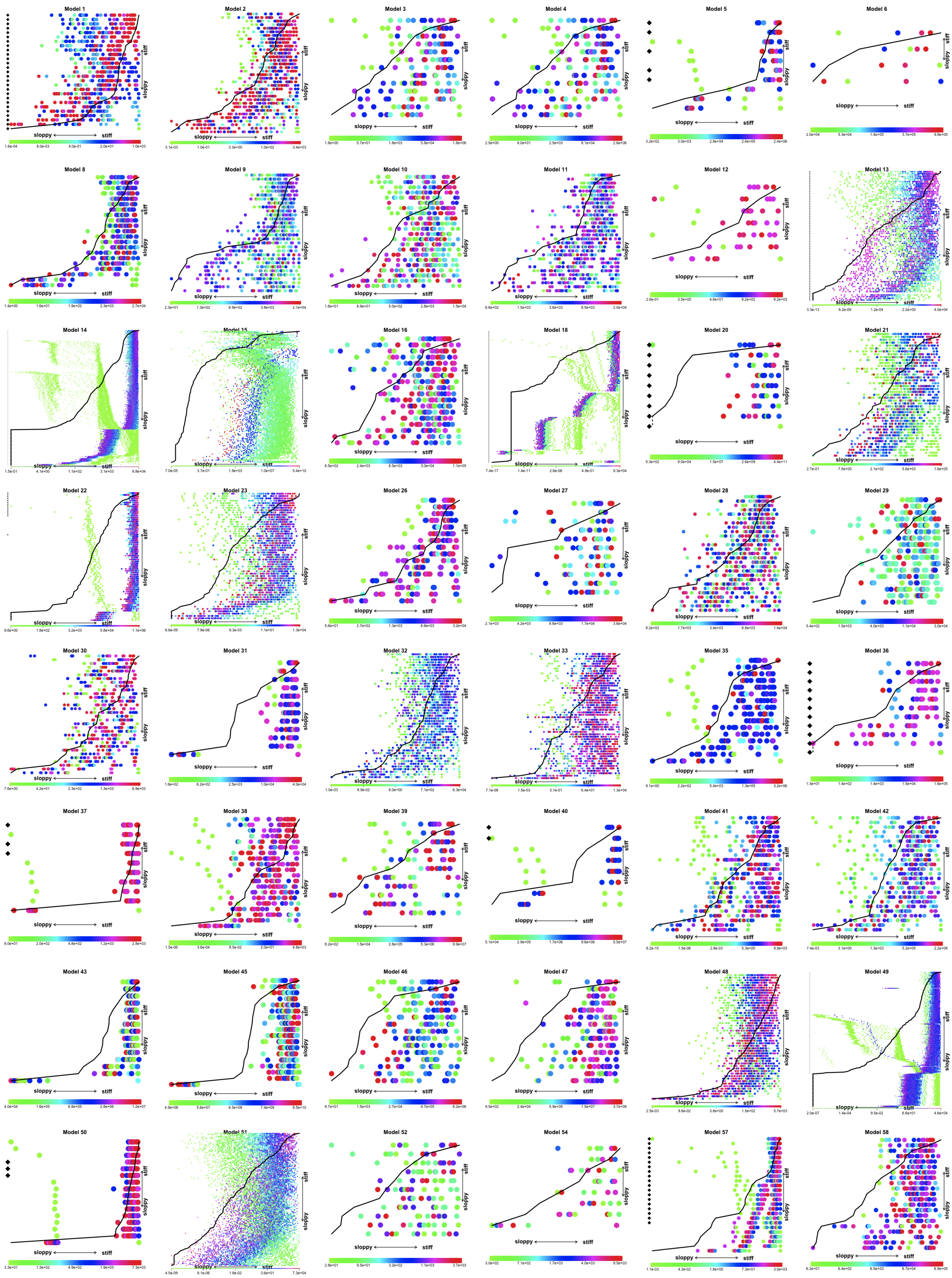
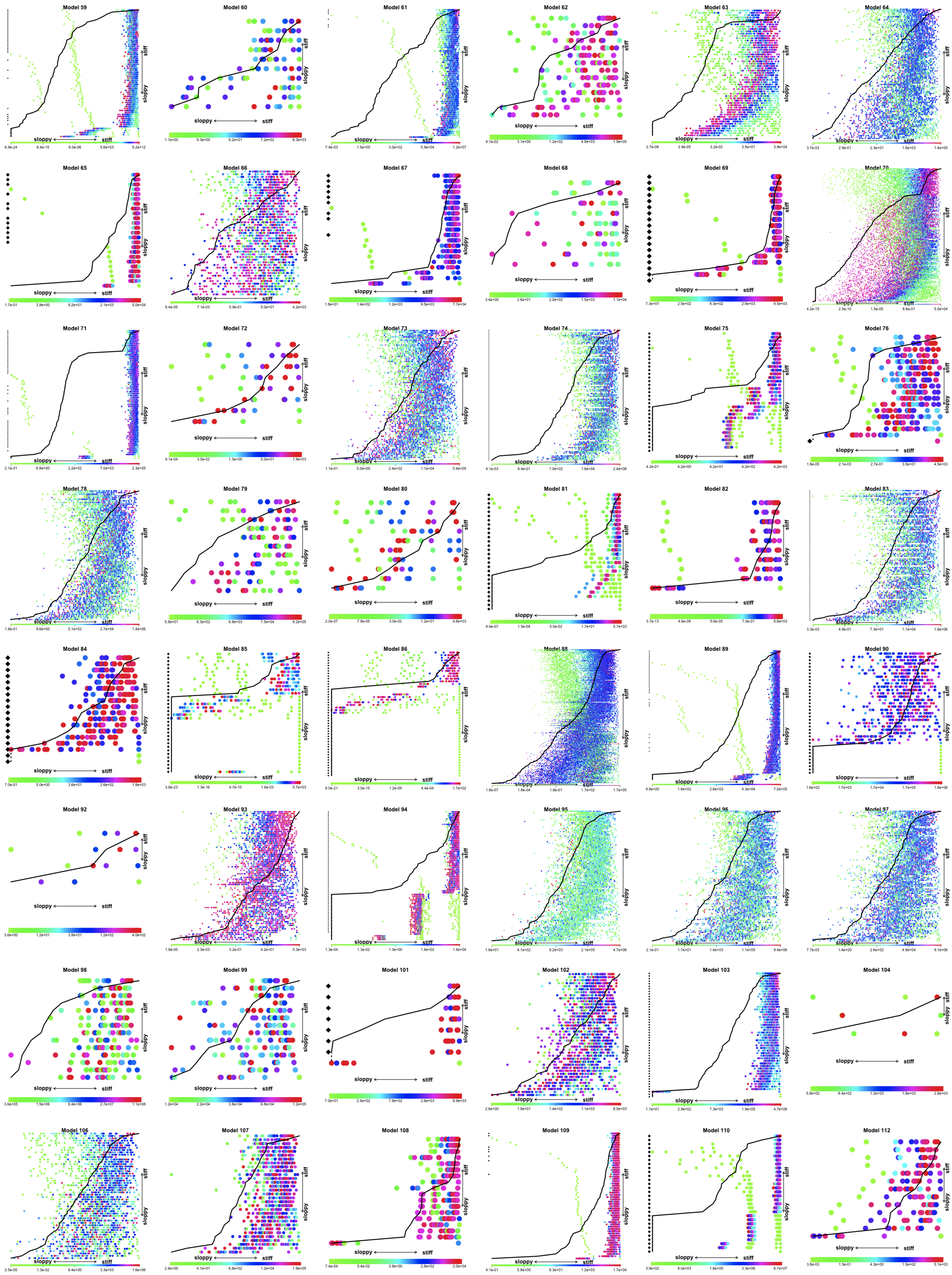


Figure SF.1: Sensitivity profiles for the BioModels database.



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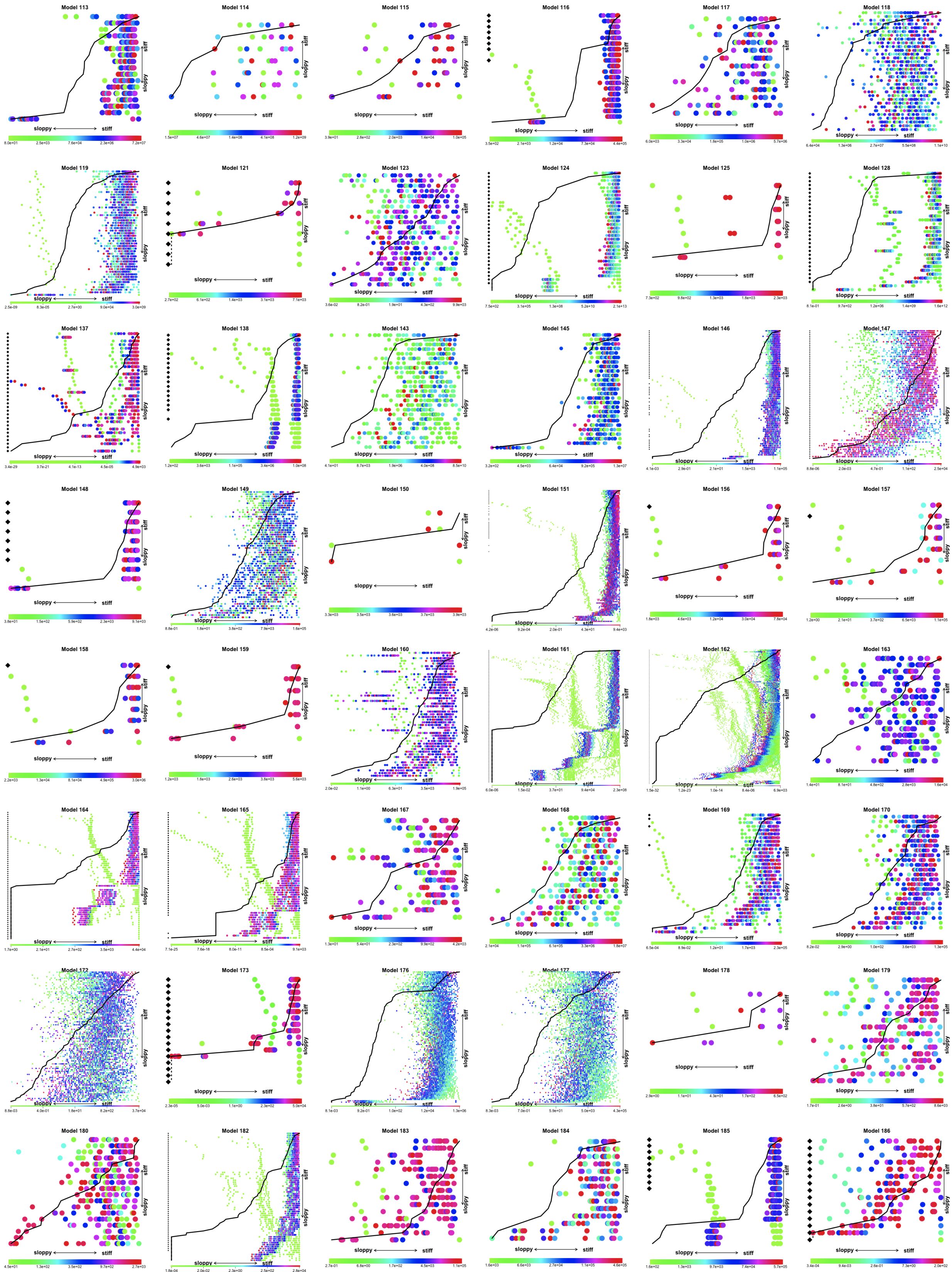

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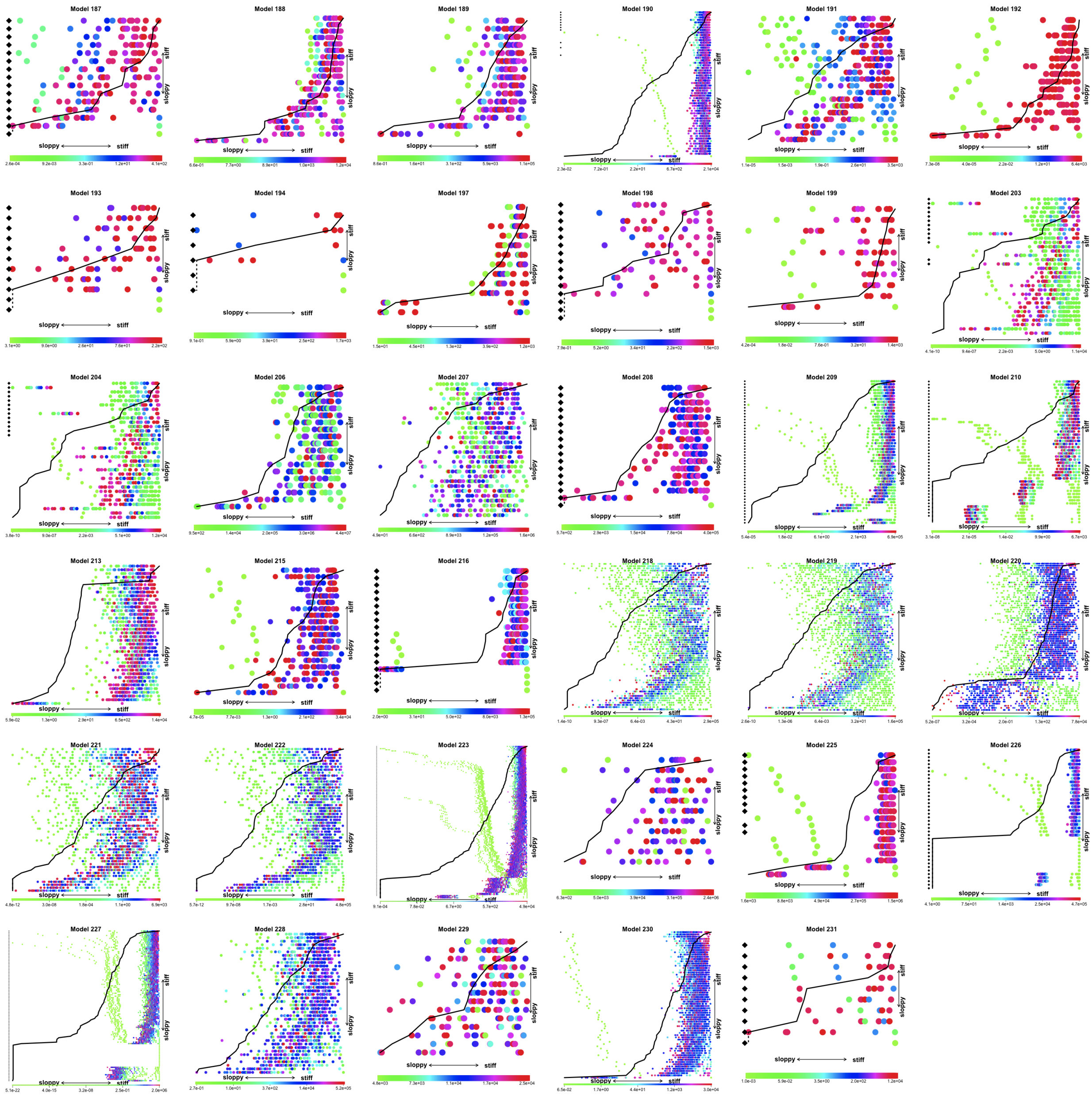

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