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Sensitivities, using the logistic model

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Logistic equation

Logistic model (where $\theta = (r, K, x_0)$):

$$\begin{aligned} \frac{dx(t;\theta)}{dt} &= rx(t;\theta)\left(1 - \frac{x(t;\theta)}{K}\right), \\ x(0;\theta) &= x_0 \end{aligned}$$

for $0 \leq t \leq 25$ (and later at $\theta = (0.7, 17.5, 0.1)$).

We can find an analytic solution:

$$x(t;\theta) = \frac{K}{1 + \left(\frac{K}{x_0} - 1\right) e^{-rt}}.$$

Sensitivities

With the closed form solution, we could just take the derivative of that model solution with respect to each parameter [2]:

$$\mathbf{s_K}(t, x(t;\theta);\theta) \triangleq \frac{\partial x}{\partial K} = \frac{x_0^2(1-e^{-rt})}{(x_0+(K-x_0)e^{-rt})^2}$$

$$\mathbf{s_r}(t, x(t;\theta);\theta) \triangleq \frac{\partial x}{\partial r} = \frac{Kx_0(K-x_0)te^{-rt}}{(x_0+(K-x_0)e^{-rt})^2}$$

$$\mathbf{r_{x_0 1}}(t, x(t;\theta);\theta) \triangleq \frac{\partial x}{\partial x_0} = \frac{K^2e^{-rt}}{(x_0+(K-x_0)e^{-rt})^2}$$

ODE form

However...

- Most problems do not admit such a nice analytic solution
- Need another solution mechanism more applicable to general ODE problems
- Take $\frac{\partial}{\partial \theta}$ in ODE form, solve resulting equations simultaneously with model (c.f., [1])

We will work with the following ODE form:

$$\frac{dx}{dt} = rx - \frac{r}{K}x^2.$$

Sensitivity for K

Take $\frac{\partial}{\partial K}$ of $\frac{dx}{dt} = rx - \frac{r}{K}x^2$:

Sensitivity for K

Take $\frac{\partial}{\partial K}$ of $\frac{dx}{dt} = rx - \frac{r}{K}x^2$:

$$\begin{aligned} \frac{\partial}{\partial K}\left(\frac{dx}{dt}\right) &= \frac{\partial}{\partial K}\left(rx - \frac{r}{K}x^2\right) \\ \Longrightarrow \frac{d}{dt}\left(\frac{\partial x}{\partial K}\right) &= r\frac{\partial x}{\partial K} - \frac{2r}{K}x\frac{\partial x}{\partial K} + \frac{r}{K^2}x^2. \end{aligned}$$

Sensitivity for K

Take $\frac{\partial}{\partial K}$ of $\frac{dx}{dt} = rx - \frac{r}{K}x^2$:

$$\begin{aligned} \frac{\partial}{\partial K}\left(\frac{dx}{dt}\right) &= \frac{\partial}{\partial K}\left(rx - \frac{r}{K}x^2\right) \\ \Longrightarrow \frac{d}{dt}\left(\frac{\partial x}{\partial K}\right) &= r\frac{\partial x}{\partial K} - \frac{2r}{K}x\frac{\partial x}{\partial K} + \frac{r}{K^2}x^2. \end{aligned}$$

Define $\mathbf{s_K} = \frac{\partial x}{\partial K}$ to be a new state. Then, we obtain the ODE

$$\frac{d}{dt}\mathbf{s_K} = r\mathbf{s_K} - \frac{2r}{K}x\mathbf{s_K} + \frac{r}{K^2}x^2.$$

For the initial condition $x(0) = x_0$, also take $\frac{\partial}{\partial K}$:

$$\frac{\partial x(0)}{\partial K} = \frac{\partial x_0}{\partial K} \quad \Longrightarrow \quad \mathbf{s_K}(0) = 0.$$

Sensitivity for r

Take $\frac{\partial}{\partial r}$ of $\frac{dx}{dt} = rx - \frac{r}{K}x^2$:

Sensitivity for r

Take $\frac{\partial}{\partial r}$ of $\frac{dx}{dt} = rx - \frac{r}{K}x^2$:

$$\begin{aligned} \frac{\partial}{\partial r}\left(\frac{dx}{dt}\right) &= \frac{\partial}{\partial r}\left(rx - \frac{r}{K}x^2\right) \\ \Longrightarrow \frac{d}{dt}\left(\frac{\partial x}{\partial r}\right) &= r\frac{\partial x}{\partial r} + x - \frac{2r}{K}x\frac{\partial x}{\partial r} - \frac{1}{K}x^2. \end{aligned}$$

Define $\mathbf{s_r} = \frac{\partial x}{\partial r}$ to be a new state. Then, we obtain the ODE

$$\frac{d}{dt}\mathbf{s_r} = r\mathbf{s_r} + x - \frac{2r}{K}x\mathbf{s_r} - \frac{1}{K}x^2.$$

For the initial condition:

$$\frac{\partial x(0)}{\partial r} = \frac{\partial x_0}{\partial r} \quad \Longrightarrow \quad \mathbf{s_r}(0) = 0.$$

Sensitivity for x_0

Take $\frac{\partial}{\partial x_0}$ of $\frac{dx}{dt} = rx - \frac{r}{K}x^2$:

Sensitivity for x_0

Take $\frac{\partial}{\partial x_0}$ of $\frac{dx}{dt} = rx - \frac{r}{K}x^2$:

$$\begin{aligned} \frac{\partial}{\partial x_0}\left(\frac{dx}{dt}\right) &= \frac{\partial}{\partial x_0}\left(rx - \frac{r}{K}x^2\right) \\ \Longrightarrow \frac{d}{dt}\left(\frac{\partial x}{\partial x_0}\right) &= r\frac{\partial x}{\partial x_0} - \frac{2r}{K}x\frac{\partial x}{\partial x_0}. \end{aligned}$$

Define $\mathbf{r_{x_0 1}} = \frac{\partial x}{\partial x_0}$ to be a new state. Then, we obtain the ODE

$$\frac{d}{dt}\mathbf{r_{x_0 1}} = r\mathbf{r_{x_0 1}} - \frac{2r}{K}x\mathbf{r_{x_0 1}}.$$

For the initial condition:

$$\frac{\partial x(0)}{\partial x_0} = \frac{\partial x_0}{\partial x_0} \qquad \Longrightarrow \qquad \mathbf{r_{x_0 1}}(0) = 1.$$

Model with sensitivities

All together:

$$\begin{aligned}
\dot{x} &= rx - \frac{r}{K}x^2 \\
\dot{\mathbf{s}}_{\mathbf{K}} &= r\mathbf{s}_{\mathbf{K}} - \frac{2r}{K}x\mathbf{s}_{\mathbf{K}} + \frac{r}{K^2}x^2 \\
\dot{\mathbf{s}}_{\mathbf{r}} &= r\mathbf{s}_{\mathbf{r}} - \frac{2r}{K}x\mathbf{s}_{\mathbf{r}} + x - \frac{1}{K}x^2 \\
\dot{\mathbf{r}}_{\mathbf{x_0 1}} &= r\mathbf{r}_{\mathbf{x_0 1}} - \frac{2r}{K}x\mathbf{r}_{\mathbf{x_0 1}}
\end{aligned}$$

with

$$x(0) = x_0, \quad \mathbf{s}_{\mathbf{K}}(0) = 0, \quad \mathbf{s}_{\mathbf{r}}(0) = 0, \quad \mathbf{r}_{\mathbf{x_0 1}} = 1.$$

You can then solve this entire system simultaneously with an ODE solver like `ode45` (or if stiff, `ode15s`).

Connection to general notation

Recall the general expression for an ODE,

$$\dot{x}(t;\theta) = g(t, x(t;\theta);\theta)$$

and the general expression for the sensitivities [1]

$$\frac{d}{dt}\left(\frac{\partial x}{\partial \theta}\right) = \frac{\partial g}{\partial x}\left(\frac{\partial x}{\partial \theta}\right) + \frac{\partial g}{\partial \theta}$$

where

$$\frac{\partial x}{\partial \theta} = \left[\frac{\partial x}{\partial q}, \ \frac{\partial x}{\partial x_0}\right] = \left[\frac{\partial x}{\partial K}, \ \frac{\partial x}{\partial r}, \ \frac{\partial x}{\partial x_0}\right] = \left[\mathbf{s_K}, \ \mathbf{s_r}, \ \mathbf{r_{x_0 1}}\right].$$

If we compute the general expression for the sensitivities above, do we get the same equations as we just obtained for $\mathbf{s_K}, \ \mathbf{s_r},$, and $\mathbf{r_{x_0 1}}$??

General notation computations

Letting $\dot{x}(t) = g(t, x; r, K, x_0) = rx - \frac{r}{K}x^2$, we compute $\frac{\partial g}{\partial x}$ and $\frac{\partial g}{\partial \theta}$:

General notation computations

Letting $\dot{x}(t) = g(t, x; r, K, x_0) = rx - \frac{r}{K}x^2$, we compute $\frac{\partial g}{\partial x}$ and $\frac{\partial g}{\partial \theta}$:

$$\begin{aligned} \frac{\partial g}{\partial x} &= \; = r - \frac{2r}{K}x \\ \frac{\partial g}{\partial \theta} &= \left[\frac{\partial g}{\partial K}, \quad \frac{\partial g}{\partial r}, \quad \frac{\partial g}{\partial x_0}\right] \\ &= \left[\frac{r}{K^2}x^2, \; x - \frac{1}{K}x^2, \; 0\right] \end{aligned}$$

Then

$$\begin{aligned} \frac{d}{dt}\left[\mathbf{s_K}, \; \mathbf{s_r}, \; \mathbf{r_{x_0 1}}\right] &= \frac{\partial g}{\partial x}\left(\frac{\partial x}{\partial \theta}\right) + \frac{\partial g}{\partial \theta} \\ &= \left(r - \frac{2r}{K}x\right)\left[\mathbf{s_K}, \; \mathbf{s_r}, \; \mathbf{r_{x_0 1}}\right] + \left[\frac{r}{K}x^2, \; x - \frac{1}{K}x^2, \; 0\right] \end{aligned}$$

which, if you multiply it out, is exactly the same as what we previously obtained (with initial conditions handled exactly as before).

Mathematical model review

We explore our experimental design questions using a mathematical model

$$\frac{d\vec{x}}{dt}(t) = \vec{g}(t, \vec{x}(t;\vec{\theta}), \vec{q}), \quad t \in [t_0, t_f] \tag{1}$$
$$\vec{x}(t_0;\vec{\theta}) = \vec{x}_0$$

- $\vec{x}(t;\vec{\theta})$: the N state variables
- $\vec{g}(t, \vec{x}, \vec{q}) : \mathbb{R}^{1+N+p} \to \mathbb{R}^N$: mathematical description of underlying process
- $\vec{x}_0$: the N initial conditions
- $\vec{q}$: the p system parameters
- $\vec{\theta}$: vector containing $p+N$ parameters and IC to estimate, contains elements from $\vec{q}$ and $\vec{x}_0$; e.g. $\vec{\theta} = [\vec{q}, \vec{x}_0]$.
- t_0, t_f: initial time, final time.

Experimental setting review

Assume we have n observations at times t_j, $j = 1, \ldots, n$, $t_0 \leq t_1 < t_2 < \ldots < t_n \leq t_f$. Introduce the observation process

$$\vec{f}(t_j; \vec{\theta}) = C(\vec{x}(t_j; \vec{\theta})), \quad j = 1, 2, \ldots, n, \tag{2}$$

where $C()$ is an observation operator that maps $\mathbb{R}^N \to \mathbb{R}^{N^*}$, $N^* \leq N$. To discuss the amount of uncertainty in parameter estimates, we formulate a statistical model [3]

$$\vec{y}_j = \vec{f}(t_j; \vec{\theta}_0) + \vec{\epsilon}(t_j), \quad j = 1, 2, \ldots, n, \tag{3}$$

where $\vec{\theta}_0$ is the true values of the unknown parameters and $\vec{\epsilon}$ represents observation error for the state variables.

Sensitivity matrix, single observable

We construct the sensitivity matrix by arranging the sensitivity equations $\frac{\partial x}{\partial \theta_k}$ in a row vector, evaluate at times $\{t_j\}_{j=1}^{n}$, and stack (to form an $n \times (p+N)$ matrix $\left(\frac{\partial x(t_j)}{\partial \theta_k}\right)$).

$$\chi_j = \begin{bmatrix} \frac{\partial x(t_1)}{\partial \theta_1} & \frac{\partial x(t_1)}{\partial \theta_2} & \cdots & \frac{\partial x(t_1)}{\partial \theta_{(p+N)}} \\ \frac{\partial x(t_2)}{\partial \theta_1} & \frac{\partial x(t_2)}{\partial \theta_2} & \cdots & \frac{\partial x(t_2)}{\partial \theta_{(p+N)}} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial x(t_n)}{\partial \theta_1} & \frac{\partial x(t_n)}{\partial \theta_2} & \cdots & \frac{\partial x(t_n)}{\partial \theta_{(p+N)}} \end{bmatrix}$$

← Need more information with more columns →

↑ More rows gives more information ↓

- Getting lots of rows is unrealistic
- Using too many columns (estimating too many parameters) may lead to bad results
- Using too few columns may not be useful

Logistic eqn sensitivity matrix

The sensitivity matrix for the logistic equation would be written as

$$\chi_j = \begin{bmatrix} \frac{\partial x(t_1)}{\partial K} & \frac{\partial x(t_1)}{\partial r} & \frac{\partial x(t_1)}{\partial x_0} \\ \frac{\partial x(t_2)}{\partial K} & \frac{\partial x(t_2)}{\partial r} & \frac{\partial x(t_2)}{\partial x_0} \\ \vdots & \vdots & \vdots \\ \frac{\partial x(t_n)}{\partial K} & \frac{\partial x(t_n)}{\partial r} & \frac{\partial x(t_n)}{\partial x_0} \end{bmatrix}$$

where the partial derivatives are as previously described

Sensitivity matrices, multiple observables

We construct sensitivity matrices by arranging the sensitivity equations $\frac{\partial f_i}{\partial \theta_k}$ in a matrix and then evaluating at times $\{t_j\}_{j=1}^{n}$ to form n sensitivity matrices, each $N^* \times (N+p)$.

$$\leftarrow \text{Need more information with more columns} \rightarrow$$

$$\chi_j = \begin{bmatrix} \frac{\partial f_1(t_j)}{\partial \theta_1} & \frac{\partial f_1(t_j)}{\partial \theta_2} & \cdots & \frac{\partial f_1(t_j)}{\partial \theta_{(p+N)}} \\ \frac{\partial f_2(t_j)}{\partial \theta_1} & \frac{\partial f_2(t_j)}{\partial \theta_2} & \cdots & \frac{\partial f_2(t_j)}{\partial \theta_{(p+N)}} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_{N*}(t_j)}{\partial \theta_1} & \frac{\partial f_{N*}(t_j)}{\partial \theta_2} & \cdots & \frac{\partial f_{N*}(t_j)}{\partial \theta_{(p+N)}} \end{bmatrix} \quad \begin{matrix} \uparrow \\ \text{More rows} \\ \text{gives more} \\ \text{information} \\ \downarrow \end{matrix}$$

- Multiple matrices: one for each time point.
- Getting lots of rows is unrealistic
- Using too many columns (estimating too many parameters) may lead to bad results
- Using too few columns may not be useful

Fisher Information Matrix

We use the sensitivity matrices to calculate the $(p+N)\times(p+N)$ Fisher Information Matrix (FIM)

$$F = \chi^{\mathsf{T}} V_0^{-1}\chi \quad \text{for single observable problems,}$$

$$F = \sum_{j=1}^{n} \chi_j^{\mathsf{T}} V_0^{-1}\chi_j \quad \text{for >1 observable problems.}$$

- F^{-1} is the covariance matrix of the parameters.
- The standard error of a parameter, $SE(\vec{\theta}_k) = \sqrt{F^{-1}_{k,k}}$, measures the reliability of its estimate.
- Off-diagonal elements of F^{-1} describe interactions between parameters.
- $F(1,1) = \sum_{j=1}^{n}\sum_{i=1}^{N^*}\left(\frac{\partial f_i(t_j)}{\partial\theta_1}\right)^2$
- $F(1,2) = \sum_{j=1}^{n}\sum_{i=1}^{N^*}\frac{\partial f_i(t_j)}{\partial\theta_1}\frac{\partial f_i(t_j)}{\partial\theta_2}$

Sources I

[1] H.T. Banks and H.T. Tran, *Mathematical and Experimental Modeling of Physical and Biological Processes*, CRC Press, Boca Raton, FL, 2009.

[2] H.T. Banks, S. Dediu, and S.E. Ernstberger, Sensitivity functions and their uses in inverse problems, *J. Inverse and Ill-posed Problems*, **15** (2007), 683–708.

[3] H. T. Banks, M. Davidian, J. R. Samuels, and K. L. Sutton. An inverse problem statistical methodology summary, CRSC Technical Report CRSC-TR08-01, NCSU, January 2008; Chapter 11 in *Statistical Estimation Approaches in Epidemiology*, Gerardo Chowell, et. al., eds. Springer, Berlin Heidelberg New York, 2009, 249–302.