Meet the Fisher information matrix (FIM)

$$M_F(\boldsymbol{\Psi}, \xi) = -\,\mathrm{E}\left[\frac{\partial^2}{\partial \boldsymbol{\Psi} \partial \boldsymbol{\Psi}^T} \log L(\boldsymbol{\Psi}; y) \middle| \boldsymbol{\Psi} \right]$$

where

- $\boldsymbol{\Psi}$ is the vector of populations parameters (e.g. `THETA`s, `OMEGA`s, and `SIGMA`s in NONMEM),
- y is the vector of observations,
- ξ is the vector of design variables (e.g. sampling times), and
- $\log L$ is the log-likelihood.

Fisher in winter coat