Simulating Onset Age Distribution of anti-GABABR Autoimmune Encephalitis from Published Summary Statistics

This Python notebook demonstrates the robustness of a statistical workflow for reconstructing age-at-onset distributions using real-world evidence from autoimmune encephalitis (AIE).

Import required library

In [95]:
```
import numpy as np
import pandas as pd
import matplotlib.pyplot as plt
import seaborn as sns
from scipy.stats import lognorm, weibull_min, gamma, genextreme # Importing neces
from scipy.optimize import minimize # Optimization for parameter fitting
from scipy.stats import probplot # Probability plot for visual assessment
from sklearn.metrics import mean_squared_error # Mean Squared Error for goodness-
from scipy.stats import gaussian_kde # Kernel Density Estimation for smooth CDF
```

Generalized Gamma

The generalized Gamma distribution has three parameters to fit:

- a: shape parameter
- c: power parameter
- scale: scale parameter

In [96]:
```
import numpy as np
from scipy.stats import gengamma
from scipy.optimize import minimize
```

In [97]:
```
median = 66
q1 = 61
q3 = 72
min = 19
max = 88
mean = 67
size = 111

empirical_q = [q1, median, q3]
```

In [98]:
```
# Define the quantile-matching objective function
def gengamma_objective(params):
    a, c, scale = params
    if a <= 0 or scale <= 0:
        return np.inf
    try:
        dist = gengamma(a=a, c=c, scale=scale)
```

```python
        theo_q = dist.ppf([0.25, 0.5, 0.75])
        return np.sum((np.array(theo_q)- np.array(empirical_q))**2)
    except:
        return np.inf
```

In [99]:
```python
# Run the optimization
initial_guess_gengamma = [2.0, 1.0, 10.0]
bounds_gengamma = [(0.01, None), (0.01, None), (0.01, None)]

result_gengamma = minimize(gengamma_objective, x0=initial_guess_gengamma, bounds=
a_fit_gengamma, c_fit_gengamma, scale_fit_gengamma = result_gengamma.x

print(f"Fitted Generalized Gamma parameters:\n a = {a_fit_gengamma:.3f}, c = {c_f
```

```
Fitted Generalized Gamma parameters:
 a = 26.611, c = 1.583, scale_fit_gengamma = 8.409
```

```
/var/folders/b8/9ymtxc2j7rb00xx34s753cwc0000gn/T/ipykernel_51726/1451994867.py:9:
RuntimeWarning: overflow encountered in square
  return np.sum((np.array(theo_q)- np.array(empirical_q))**2)
/opt/anaconda3/lib/python3.12/site-packages/scipy/optimize/_numdiff.py:590: Runti
meWarning: invalid value encountered in subtract
  df = fun(x) - f0
```

In [100…
```python
# Simulate and visualize
import matplotlib.pyplot as plt
```

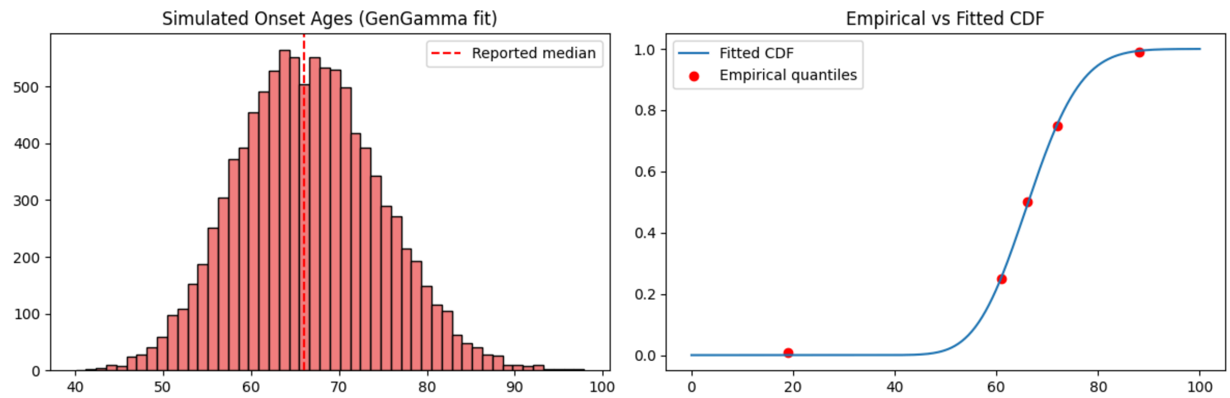
In [101…
```python
# Simulate onset ages
sim_ages_gengamma = gengamma(a = a_fit_gengamma, c = c_fit_gengamma, scale = scal
```

In [102…
```python
# Plot histogram and CDF
fig, ax = plt.subplots(1, 2, figsize = (12, 4))

# Histogram
ax[0].hist(sim_ages_gengamma, bins=50, color='lightcoral', edgecolor='black')
ax[0].axvline(x=median, color='red', linestyle='--', label='Reported median')
ax[0].set_title('Simulated Onset Ages (GenGamma fit)')
ax[0].legend()

# CDF
x_gengamma = np.linspace(0, 100, 300)
model_cdf_gengamma = gengamma(a=a_fit_gengamma, c=c_fit_gengamma, scale=scale_fit
ax[1].plot(x_gengamma, model_cdf_gengamma, label='Fitted CDF')
ax[1].scatter([min, q1, median, q3, max], [0.01, 0.25, 0.5, 0.75, 0.99], color='r
ax[1].set_title('Empirical vs Fitted CDF')
ax[1].legend()

plt.tight_layout()
plt.show()
```



In this case, the Generalized Gamma distribution shows the smallest squared difference, indicating the best fit among the three candidate distributions.

Sensitivity analysis with Monte Carlo simulation

Purpose

The current sensitivity analysis based on a fixed ±10% grid has notable limitations.

To address these, I plan to implement Monte Carlo simulation using fitted distribution parameters, which offers three key advantages:

- Continuous uncertainty representation rather than relying on only low, central, and high values.
- Faster and smoother calculations through the cumulative distribution function (CDF), without the need for inner resampling.
- More stable confidence intervals and compatibility with tornado analysis for identifying key drivers.

Procedure

1. Draw N parameter triplets from continous priors distributions.
2. Use CDF differences to get exact band probabilities per draw.
3. Aggregate acroos draws to get mean, median and 95% CI.

Code for implementation

In [103…

```
import numpy as np
import pandas as pd
from scipy.stats import gengamma, norm
```

In [104…

```
# The fitted model object from previous analysis
result_gengamma
```

Out[104...
```
  message: CONVERGENCE: REL_REDUCTION_OF_F_<=_FACTR*EPSMCH
  success: True
   status: 0
      fun: 0.10243077858152738
        x: [ 2.661e+01  1.583e+00  8.409e+00]
      nit: 88
      jac: [-1.463e-02  1.069e+00 -8.571e-02]
     nfev: 456
     njev: 114
 hess_inv: <3x3 LbfgsInvHessProduct with dtype=float64>
```

In [106...
```
# Get the MLE
theta_hat = result_gengamma.x

print(theta_hat)
```

```
[26.61103626  1.58349596  8.40915197]
```

Compute the Hessian numerically at the optimum

In [107...
```
import numpy as np
from statsmodels.tools.numdiff import approx_hess

H = approx_hess(theta_hat, gengamma_objective)  # by default, central differences
```

In [108...
```
# Invert the Hessian to get the variance-covariance matrix
vcov_matrix = np.linalg.inv(H)

print(vcov_matrix)
```

```
[[ 5.95129550e+02 -1.77608293e+01 -3.15062237e+02]
 [-1.77608293e+01  5.51055889e-01  9.63377691e+00]
 [-3.15062237e+02  9.63377691e+00  1.69340808e+02]]
```

In [109...
```
# Multivariate normal sampling on fitted scale

from numpy.random import default_rng
rng = default_rng(123)
N = 5000

m = theta_hat  # MLE parameter vector
L = np.linalg.cholesky(vcov_matrix)  # Cholesky decomposition of variance-covaria
Z = rng.standard_normal((N, len(m)))  # Standard normal samples

theta_draws = m + Z @ L.T  # MVN samples of parameters
mu_draws, log_sigma_draws, Q_draws = theta_draws.T
```

In [110...
```
np.mean(log_sigma_draws)
```

Out[110...
```
1.5637918813315672
```

In [111...
```
# Age bands (inclusive of lower, exclusive of upper)
age_bands = [(0, 12), (12, 18), (18, 100)]
```

This custom function aims to calculate log-scale standard deviation for a log-normal prior, so that approximately 95% of mass falls with ±10% multiplicative of the median.

Derivation

For Y ~ Normal(mu, sigma) the 95% interval is mu ± 1.96sigma, so on the orignal scale exp(mu ± 1.96sigma) gives a multiplicative factor exp(1.96*sigma). Setting that factor = 1.1 (i.e. +10%) give sigma = ln(1.1)/ 1.96

rng.lognormal() is a NumPy random number generator method that draws samples from a log-normal distribution - a distribution where the logarithm of the variable follows normal (Gaussian) distribution.

rng.lognormal(mean=mu_a, sigma=s_log, size=N) draws samples X = exp(Y) where Y ~ Normal(mu_a, s_log)

Note that rng.lognormal equivalent to np.exp(rng.normal(mean, sigma, size))

In [112…
```
# Compute band probabilities for each parameter set via CDF
def band_probs_for_draw(a, c, s):
    F = gengamma(a=a, c=c, scale=s).cdf
    p0_12 = F(12.0) - F(0.0)
    p12_18 = F(18.0) - F(12.0)
    p18_100 = F(100.0) - F(18.0)
    return p0_12, p12_18, p18_100
```

gengamma(a=a, c=c, scale=s) constructs a "frozen" SciPy generalized Gamma distribution with given parameters. Appending .cdf returns that distribution's cumulative distribution function as a callable (i.e., can be called like a function).

What F is: a function F(x) that returns P(x <= x) for X ~ GenGamma(a,c,scale=s). It accepts acalars or numpy arrays and returns probabilities in [0,1].

In [113…
```
P = np.array([band_probs_for_draw(a, c, s) for a, c, s in zip(mu_draws, log_sigma
```

In [114…
```
print(P[:10])
```

```
[[1.20059387e-02 7.33904212e-02 9.14603640e-01]
 [1.08145832e-25 8.45280534e-18 9.99985839e-01]
 [1.92092384e-12 1.54251855e-08 9.99999974e-01]
 [1.20756676e-18 5.23993223e-13 9.99994565e-01]
 [           nan            nan            nan]
 [1.70337946e-27 3.55365476e-19 9.99994112e-01]
 [3.04377245e-19 1.99256162e-13 9.99996554e-01]
 [1.00000000e+00 2.01283434e-13 0.00000000e+00]
 [           nan            nan            nan]
 [           nan            nan            nan]]
```

In [115…
```
# Filter out NaNs in all three columns
P = P[~np.isnan(P).any(axis=1)]
```

In [116…
```
print(P[:10])
```

```
[[1.20059387e-02 7.33904212e-02 9.14603640e-01]
 [1.08145832e-25 8.45280534e-18 9.99985839e-01]
 [1.92092384e-12 1.54251855e-08 9.99999974e-01]
 [1.20756676e-18 5.23993223e-13 9.99994565e-01]
 [1.70337946e-27 3.55365476e-19 9.99994112e-01]
 [3.04377245e-19 1.99256162e-13 9.99996554e-01]
 [1.00000000e+00 2.01283434e-13 0.00000000e+00]
 [8.17154984e-16 4.93084700e-11 9.99937577e-01]
 [1.00000000e+00 0.00000000e+00 0.00000000e+00]
 [2.02810919e-20 2.75611355e-14 9.99997395e-01]]
```

In [117…

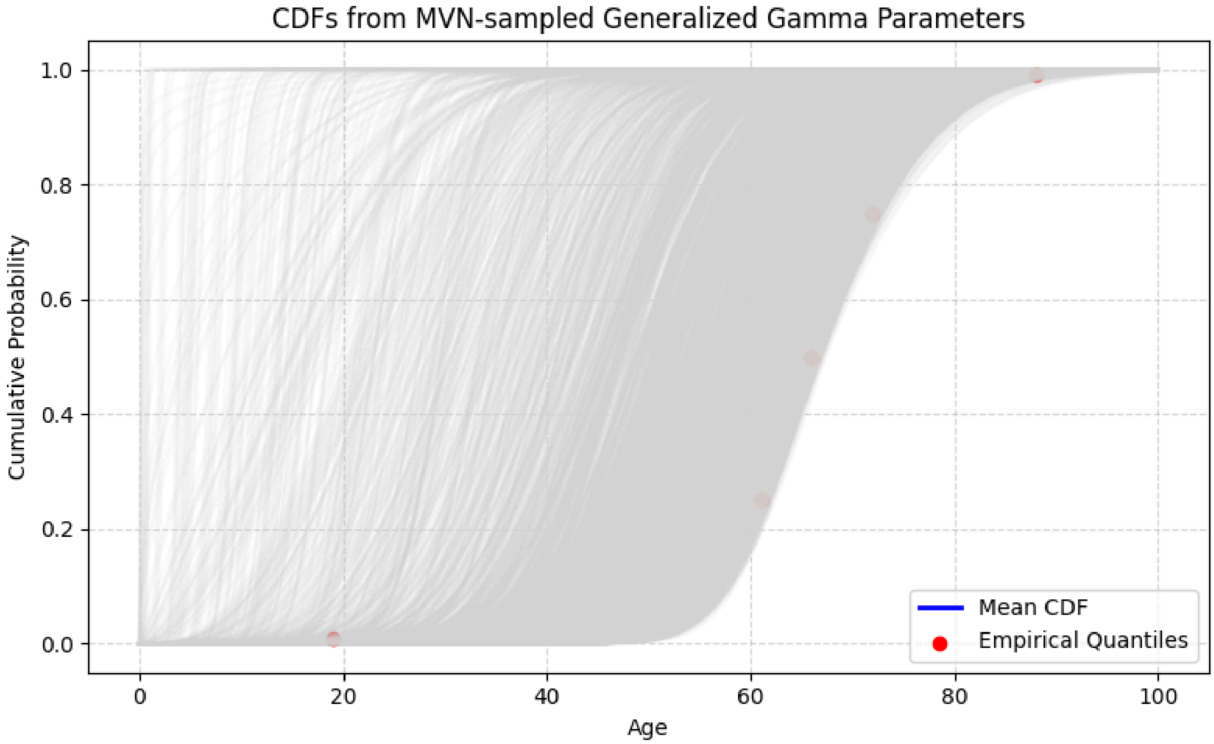
```
# Summarize reults
summary = pd.DataFrame({
    'Age Band': ['0-12', '12-18', '18+'],
    'Mean': np.char.mod('%.2f%%', P.mean(axis=0)*100),
    "SD": np.char.mod('%.2f%%', P.std(axis=0)*100),
    "Median": np.char.mod('%.2f%%', np.median(P, axis=0)*100),
    "CI Lower (2.5%)": np.char.mod('%.2f%%', np.percentile(P, 2.5, axis=0)*100),
    "CI Upper (97.5%)": np.char.mod('%.2f%%', np.percentile(P, 97.5, axis=0)*100)
})

print(summary)
```

```
  Age Band    Mean      SD   Median CI Lower (2.5%) CI Upper (97.5%)
0     0-12   2.67%  14.00%    0.00%           0.00%           44.47%
1    12-18   1.95%   9.41%    0.00%           0.00%           23.81%
2      18+  95.38%  18.45%  100.00%           9.54%          100.00%
```

In [118…

```
# Draw CDF for sampled parameters
x = np.linspace(0, 100, 300)
cdf_samples = [gengamma(a=a, c=c, scale=s).cdf(x) for a, c, s in zip(mu_draws, lo
import matplotlib.pyplot as plt
# Plot sampled CDFs
plt.figure(figsize=(8, 5))
for cdf in cdf_samples:
    plt.plot(x, cdf, color='lightgray', alpha=0.1)
# Plot mean CDF
mean_cdf = np.mean(cdf_samples, axis=0)
plt.plot(x, mean_cdf, color='blue', label='Mean CDF', linewidth=2)
# Plot empirical quantiles
plt.scatter([min, q1, median, q3, max], [0.01, 0.25, 0.5, 0.75, 0.99], color='rec
# Format plot
plt.title('CDFs from MVN-sampled Generalized Gamma Parameters')
plt.xlabel('Age')
plt.ylabel('Cumulative Probability')
plt.legend()
plt.grid(linestyle='--', alpha=0.5)
plt.tight_layout()
plt.show()
```


CDFs from MVN-sampled Generalized Gamma Parameters
Cumulative Probability
0.0
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
100
Age
Mean CDF
Empirical Quantiles