# POPULATION MODELING APPROACH OF CIRCADIAN BLOOD PRESSURE VARIATIONS USING AMBULATORY MONITORING IN DIPPERS AND NON DIPPERS


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## Introduction

✓In most patients with essential hypertension, blood pressure (BP) decreases by 10 to 30% at night compared to daytime values. Nevertheless, in about 30% of the hypertensive population, patients termed "non dipper" present a blunted night-time decrease in BP and are particularly at risk regarding target organ damage.

✓This nocturnal BP fall is calculated as a relative reduction in average BP at night (11 PM to 06:59 AM) compared to daytime (7 AM to 10:59 PM) values for both systolic and diastolic BP (respectively SBP and DBP) that means without using the whole ABPM information.

✓ Non dippers were defined as those with a nocturnal BP fall in SBP, DBP or both < 10% of daytime BP, leading to split the hypertensives into 2 subpopulations: dippers and non dippers.

✓As this categorization was only based on a clinical definition, we were interested in investigating if any heterogeneity in the global population can be explained using many subpopulations.

**Thus the aim of the present work was to evaluate the ability of a mixture model to correctly predict the clinical dipper status.**

## Data

✓Data were extracted from a placebo run-in phase of a large randomized clinical trial in 1004 mild to moderate essential hypertensives.

✓Diabetic patients were excluded.

✓According to the gold standard dipping definition there are 649 dippers and 355 non dippers on SBP.

## Mixture distribution modeling

✓k is the number of subpopulations fixed to 2. The probability that an individual drawn from a population is a member of the kth subpopulation is $p_k$.

✓This probability $p_k$ can be interpreted as the proportion (P) of patients in one type of population.

✓As we have no prior knowledge of which combination of parameters is involved in the nocturnal BP fall, different mixture models were tested.

## Structural model

✓Based on prior knowledge, a 3 cosine model (as follows) best described BP circadian variations.

$$BP(t) = \theta_1 \times \exp(\eta_1) \times \left[ 1 + \left( \sum_{i=1}^{3} \theta_{2i} \times \exp(\eta_{2i}) \times \cos\left( i \times 2\pi / 24 \times (t - (\theta_{2i+1} + \eta_{2i+1})) \right) \right) \right] + \varepsilon$$

$\theta_1$ is mesor (mean over the 24 hours), $\theta_{2i}$ are amplitudes and $\theta_{2i+1}$ are phase shifts of the cosine terms.

$\eta_1$, $\eta_{2i}$ and $\eta_{2i+1}$ represent interindividual variabilities of the mesor, amplitudes and phase shifts, respectively.

Interindividual variability was found on mesor and amplitudes (multiplicative model) and on phase shifts (additive model).

$\varepsilon$ represents the additive residual error.

## Model evaluation

✓The selection of the final model was both based on Likelihood Ratio Test (LRT) and on the percentage of misclassified patients by the model regarding the gold standard definition.

✓Data were analyzed using NONlinear Mixed Effects Modelling (NONMEM version V) with the FOCE (First Order Conditional Estimate) method with interaction.

## Results from the mixture model

As the results were similar between DBP and SBP, only those for SBP are reported here.

**Table 1. Population parameters of the final SBP mixture model in the two subpopulations.**

| | Mean parameter estimate (%CVSE) | | Interindividual variability (%CVSE) | |
|---|---|---|---|---|
| | Population 1 | Population 2 | Population 1 | Population 2 |
| Mesor (mmHg) | 138 (0.4) | 145 (0.8) | 9.2 (7.1) | 11 (9.2) |
| Amplitude cos1 | 10% (2.8) | 5% (6.4) | 33 (10) | 51 (11) |
| Phase shift cos1 | 15 (0.5) | 14 (1.8) | 1.4 (14) | 3.9 (13) |
| Amplitude cos2 | 5.4%(2.6) | 3.8%(6.8) | 37 (11) | 57 (16) |
| Phase shift cos2 | 8.9 (0.5) | | 1.3 (8.2) | |
| Amplitude cos3 | 2.6%(2.5) | | 47 (8.8) | |
| Phase shift cos3 | 2.5 (2.8) | 1.9 (6.8) | 1.2 (14) | 1.6 (11) |
| Residual error (mmHg) | 11 (1.4) | | | |
| Proportion population 2 | 0.34 (12) | | | |

Estimates of amplitudes of the cosine terms are expressed as a percentage of the mesor. Estimates of interindividual variability (IIV) of mesor and amplitude are expressed as coefficient of variation. Interindividual variability of phase shift is expressed in hours. %CVSE is Coefficient of Variation based on Standard Error.

**Table 2. The main different assumptions tested to build the mixture model.**

| Mixture model description | Likelihood ratio | Number of parameters |
|---|---|---|
| No mixture | - | 15 |
| Mixture on amplitude cos2 | -159 | 18 |
| Mixture on mesor and amplitude cos2 | -171 | 20 |
| Mixture on mesor , 2 amplitudes and 2 phase shits | -506 | 26 |

**Table 3. Percentage of misclassified patients in the different mixture models tested.**

| Mixture model description | Percentage of misclassified patients |
|---|---|
| Mixture on amplitude cos2 | 24.7% |
| Mixture on mesor and amplitude cos2 | 24.2% |
| Mixture on 2 amplitudes and 2 phase shits | 9.7% |

Percentage of misclassified patients is expressed as the proportion of false positives and false negatives within the population.

## Discussion and conclusion

✓The use of a mixture model to deal with the variability of the nocturnal blood pressure fall was found to be relevant in terms of decrease of the objective function value.

✓The best model was the model including mixture on parameters which were previously found significantly different between dippers and non dippers.

✓The low percentage of misclassified patients shows the ability of the model to classify the hypertensives in the two clinical subpopulations.

✓Estimation of parameters by the mixture model reproduces quantitatively the differences previously observed in mesor and amplitudes in the two clinical subpopulations.

✓Dipping status categorization is not only clinical but also statistical.

✓Further models are currently tested regarding the ability to decrease the proportion of misclassified patients.


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