NCC: An R-package for analysis and simulation of platform trials with non-concurrent controls

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"NCC: An R-package for analysis and simulation of platform trials with non-concurrent controls". (2023). `https://arxiv.org/abs/2302.12634`

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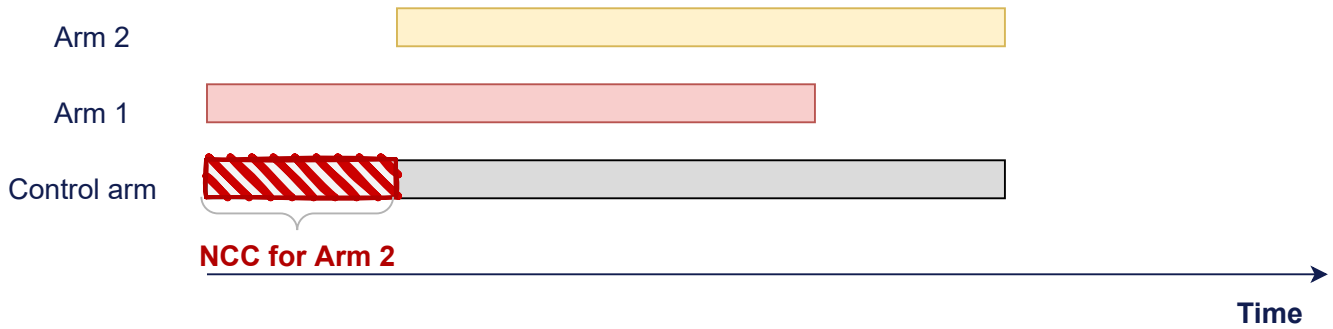
Introduction

Platform trials

Multi-arm adaptive trials that allow experimental treatment arms to enter and leave the trial at different times

Control groups in platform trials:

- **Concurrent controls (CC):** patients recruited to the control when the experimental treatment is part of the platform
- **Non-concurrent controls (NCC):** patients recruited before the experimental treatment entered the platform



Challenges when using NCC in the presence of time trends:

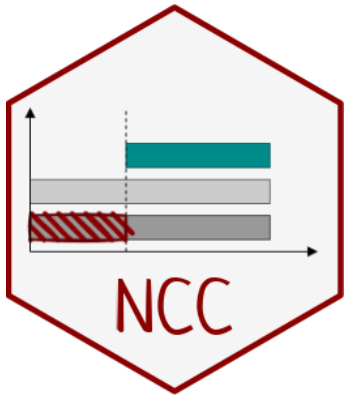
- Bias in the estimates
- Type I error rate control

→ **Modelling approaches**

NCC R-package

Aims:

- Simulate platform trials with shared controls in the presence of time trends
- Analyze data using various methods for incorporating NCC
- Perform simulation studies to evaluate and compare the performance of the methods



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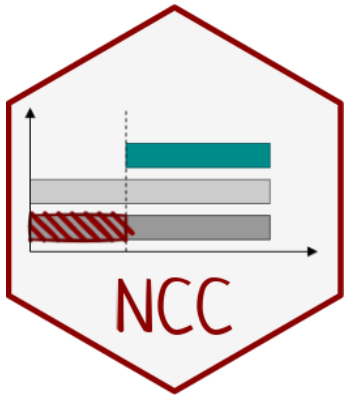


Data generation:

- Functions to simulate a platform trial with continuous or binary outcome

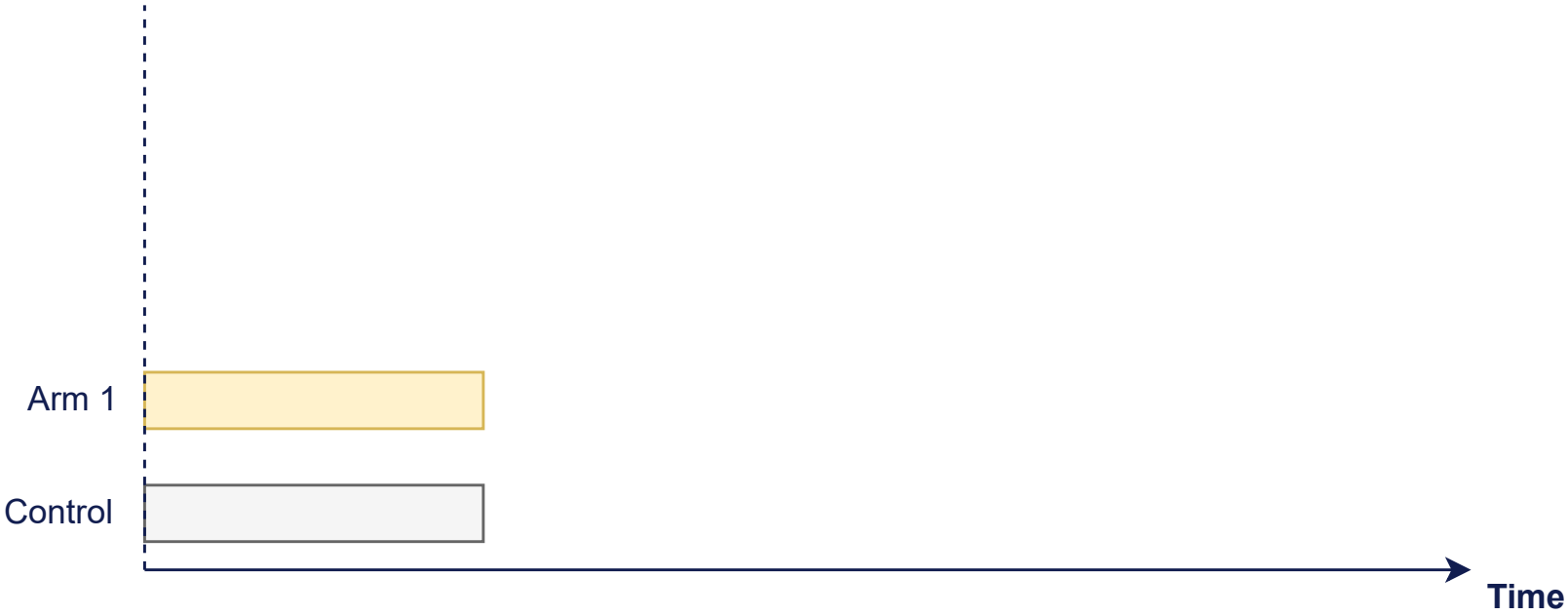
Analysis approaches:

- Regression models with fixed effects
- Time Machine model
- MAP prior approach
- Pooled and separate analysis

Wrapper functions:

- Functions to run simulations in parallel and evaluate the operating characteristics of the implemented methods

Motivating trial design



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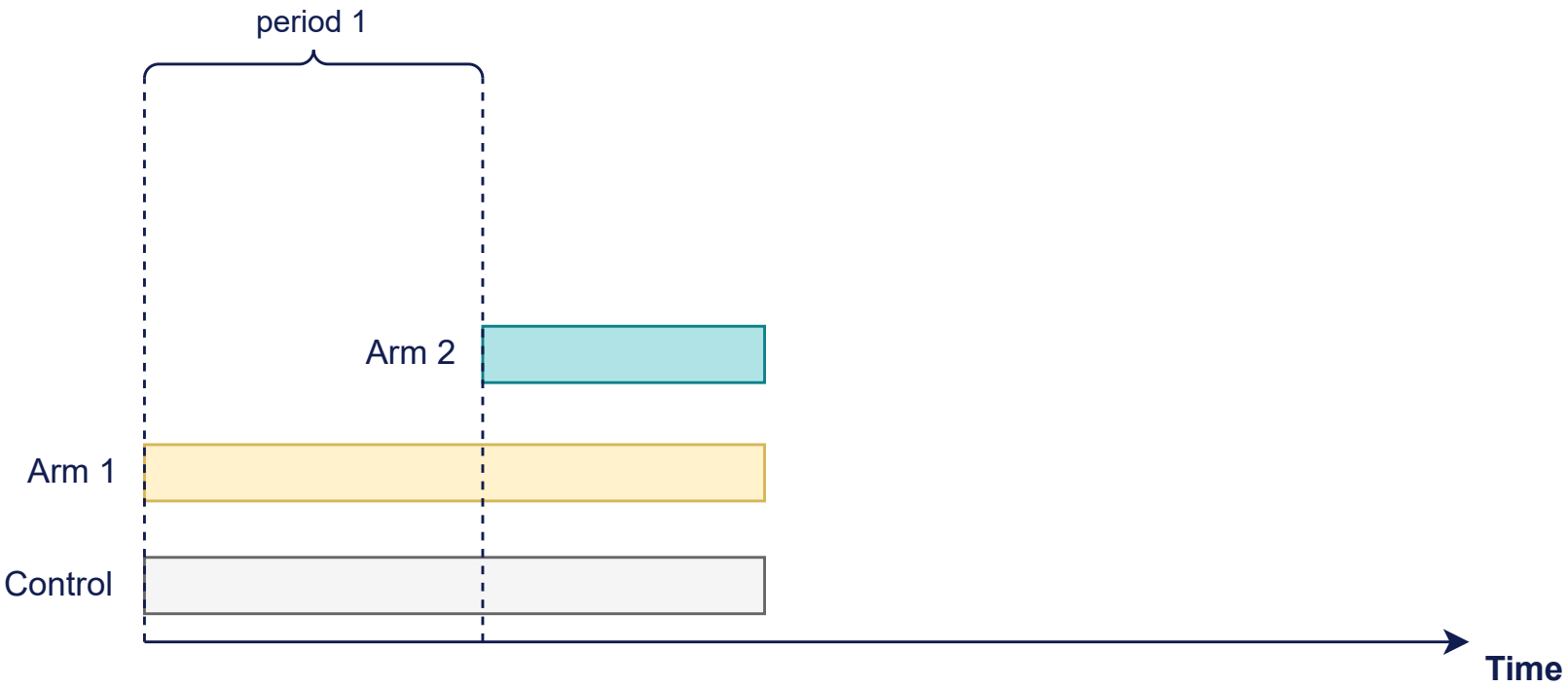

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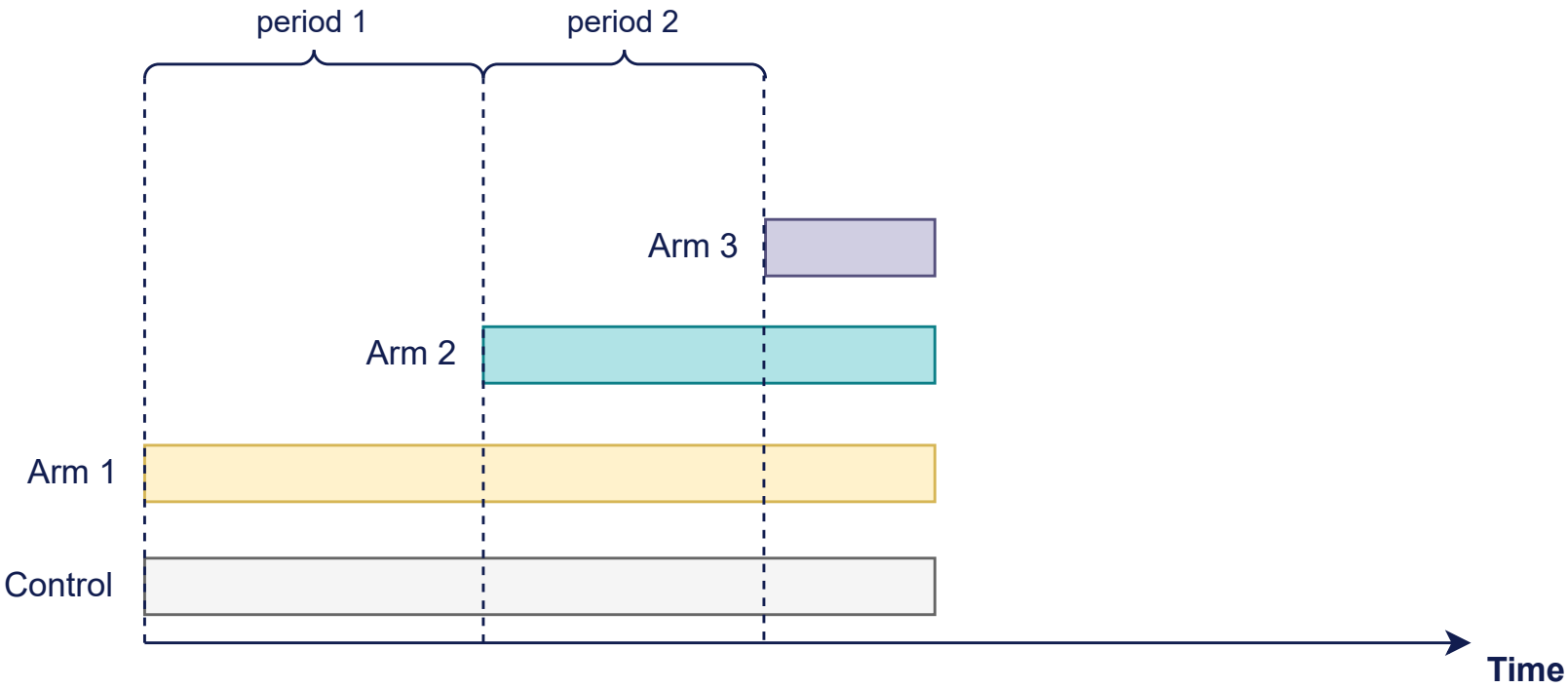

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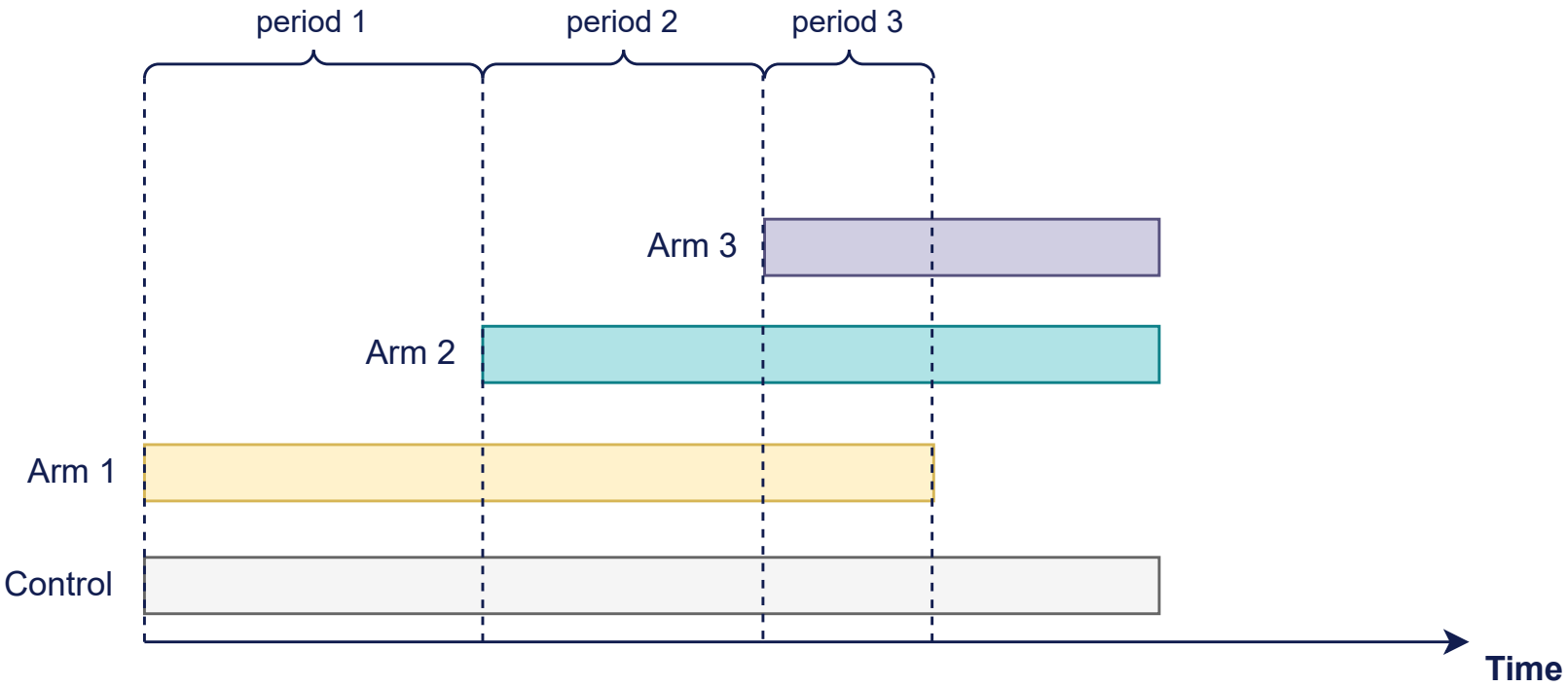

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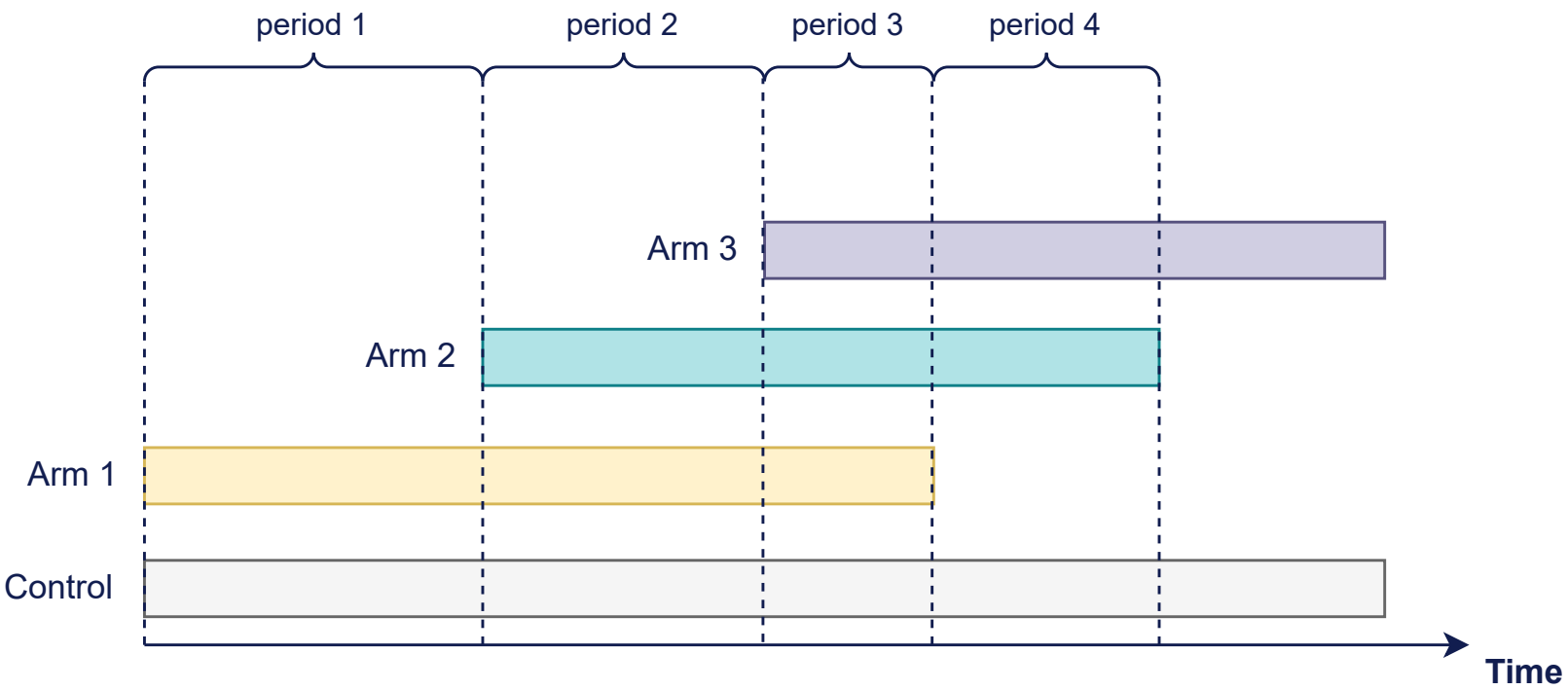

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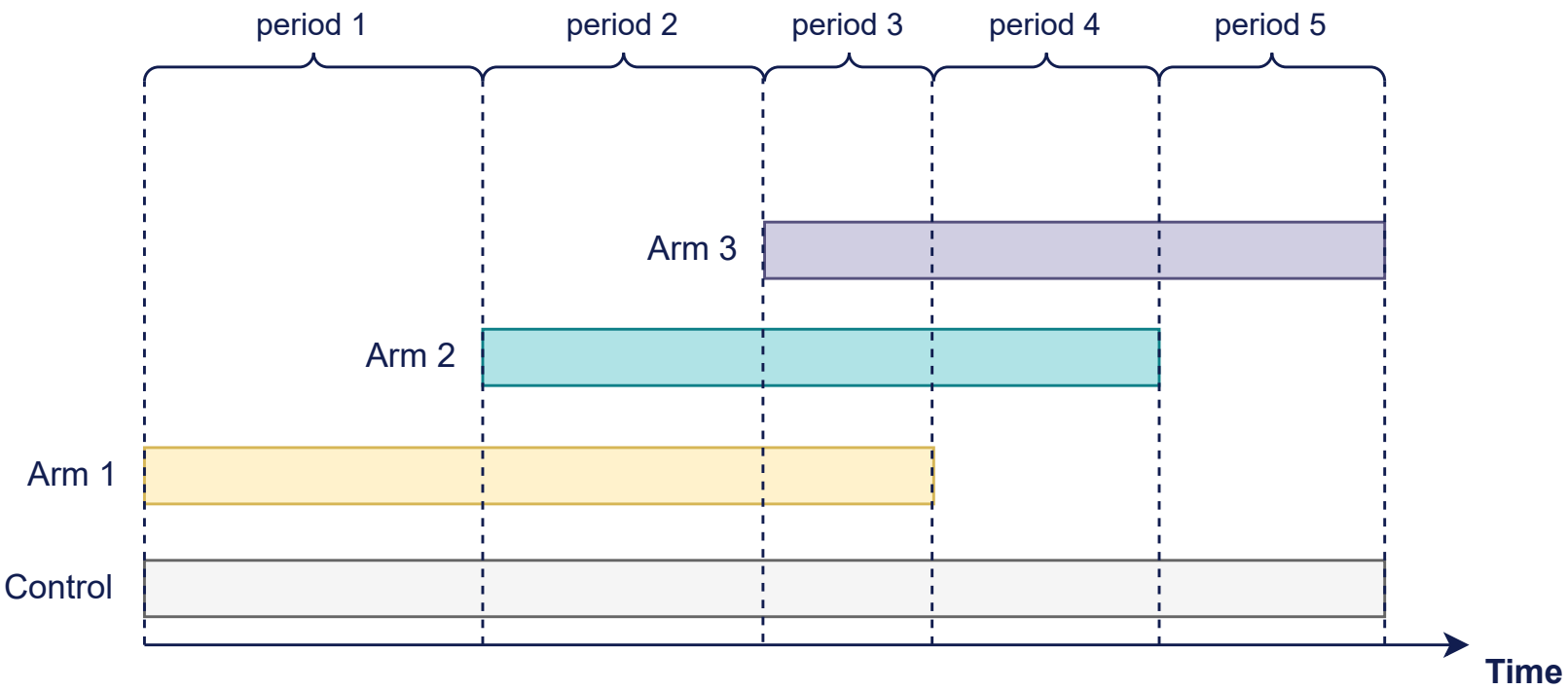
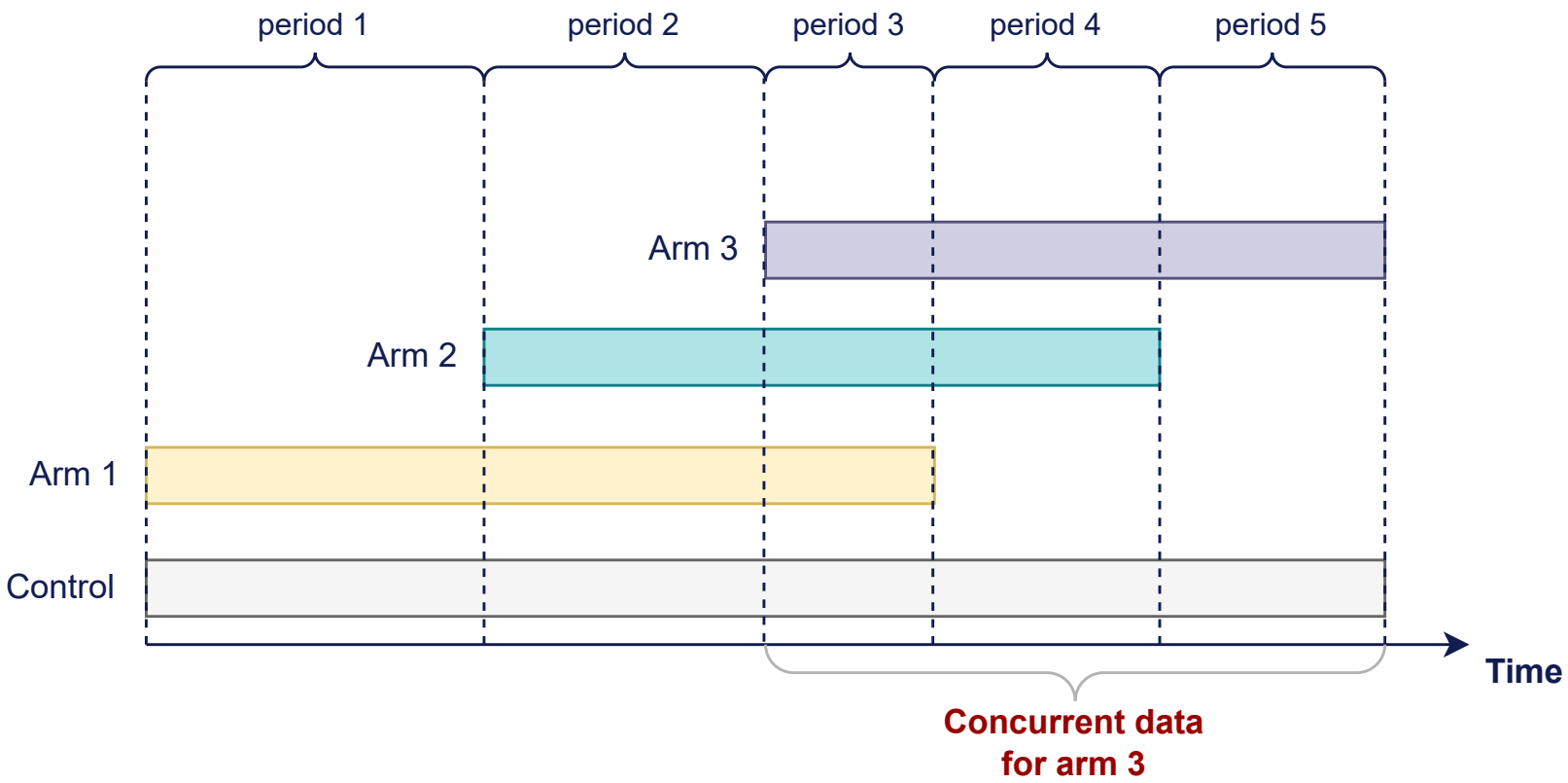


Hypothesis testing problem:

$$H_0 : \theta_3 = 0$$
$$H_1 : \theta_3 > 0$$

Motivating trial design



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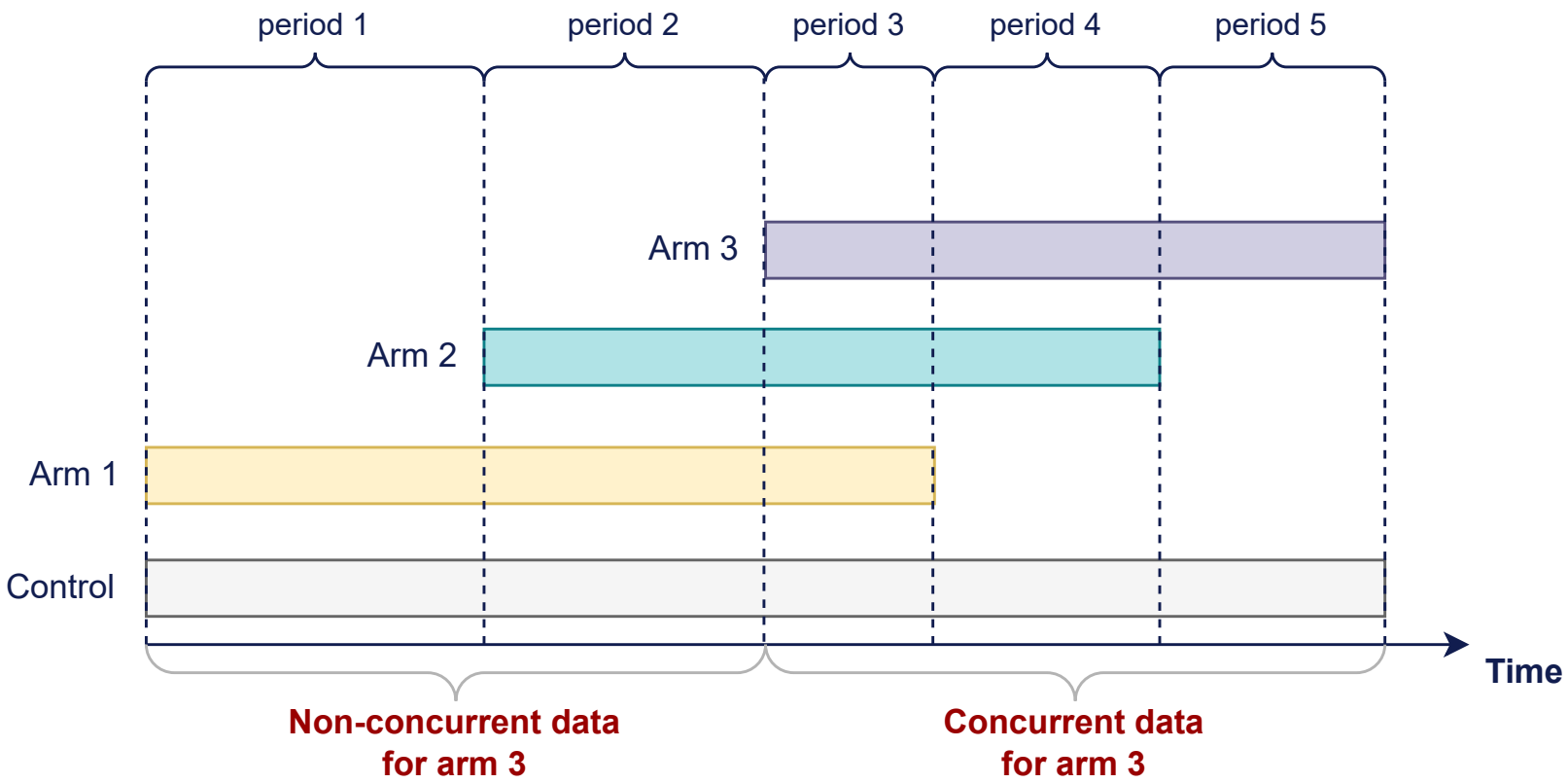


Hypothesis testing problem:

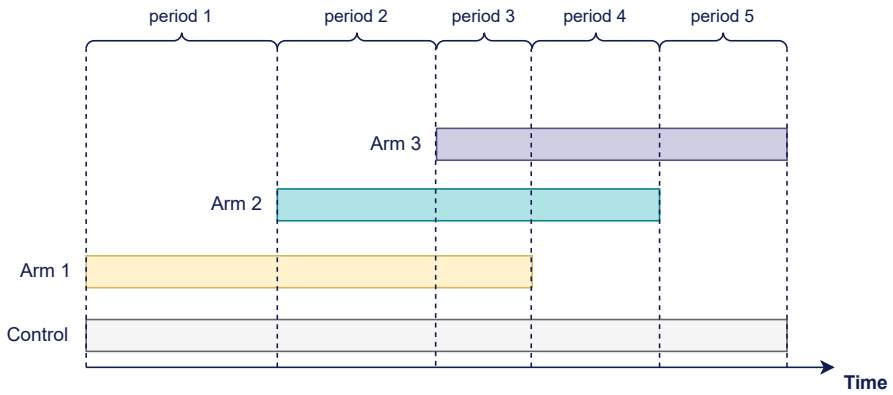
$$H_0 : \theta_3 = 0$$
$$H_1 : \theta_3 > 0$$

How to simulate data from a platform trial using the NCC package

Simulating a platform trial with binary endpoints:

```
datasim_bin(num_arms = 3, n_arm = 250, d = c(0, 250, 500),
            p0 = 0.5, OR = c(1.65, 1.65, 1.65),
            trend = "linear", lambda = c(0.15, 0.15, 0.15, 0.15))
```

- Platform trial with 3 experimental treatment arms in total
- Sample sizes of 250 in each experimental treatment arm
- Arms 2 and 3 entering after 250 and 500 patients have been recruited
- Control response at the start of the trial of 0.5 and odds ratios of 1.65 in each experimental treatment arm
- Block randomization with $1 : 1 : \ldots : 1$ allocation rates is used to assign patients to the active arms



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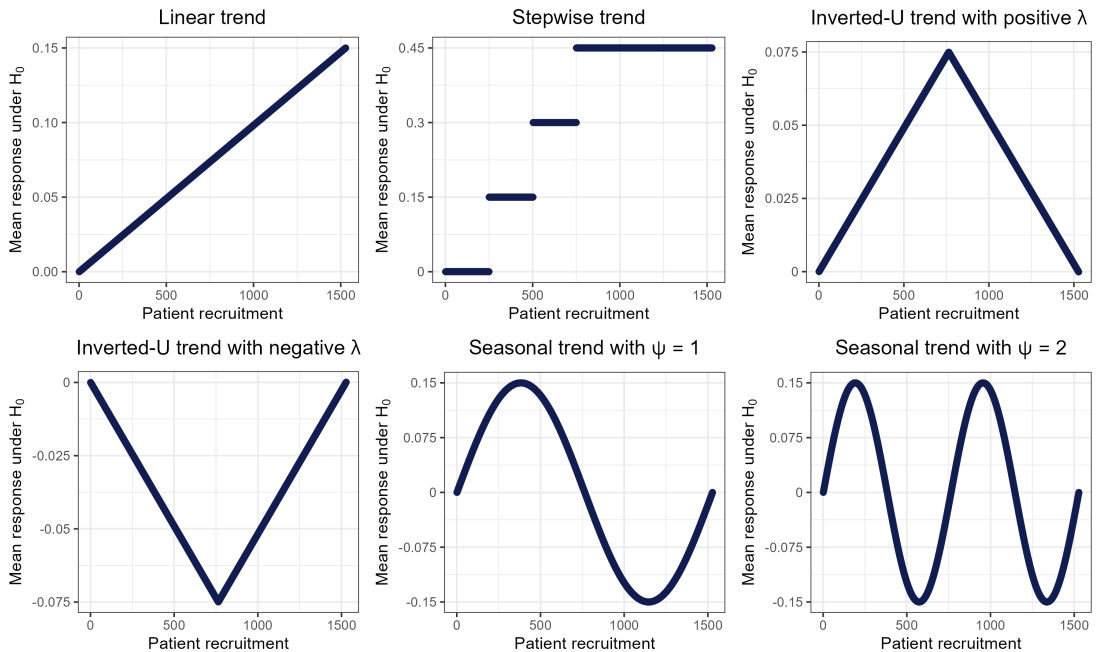
```

- Linear time trend of strength 0.15 in each arm



Analogous function for continuous endpoints: `datasim_cont()`

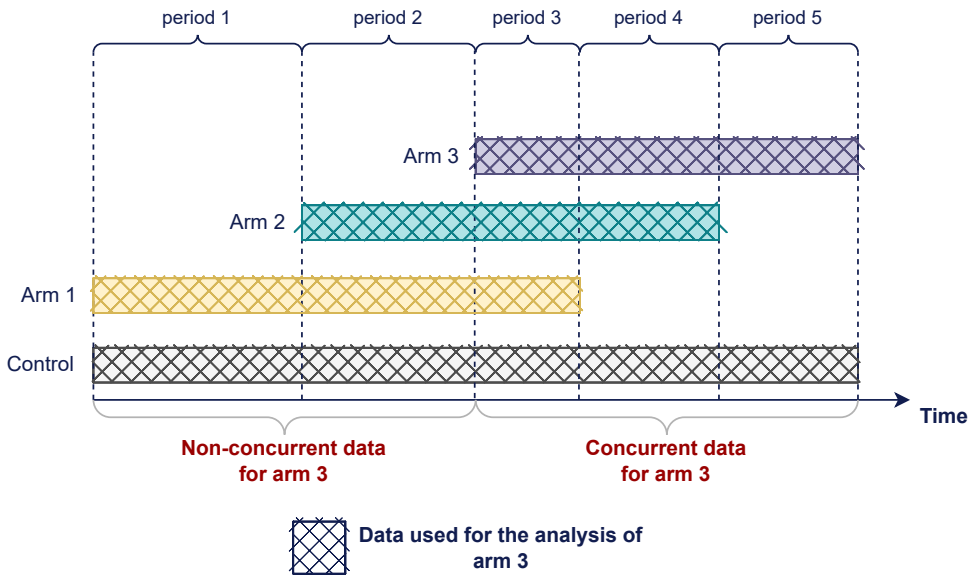
Modelling approaches – Frequentist model-based approach

Adjusts for time trends by adding time as a covariate into the regression model[1]:

$$g(E(y_j)) = \eta_0 + \sum_{k=1}^{3} \theta_k \cdot I(k_j = k) + \sum_{s=2}^{5} \tau_s \cdot I(s_j = s)$$

Notation:

- y_j ... response for patient j
- η_0 ... control response in the first period
- k_j ... treatment arm patient j is allocated in
- s_j ... period patient j was recruited in
- θ_k ... treatment effect of treatment arm k
- τ_s ... time effect in period s



[1] Bofill Roig, M., Krotka, P., et al. (2022). On model-based time trend adjustments in platform trials with non-concurrent controls. BMC Medical Research Methodology.

Modelling approaches – Frequentist model-based approach

Implementation in the NCC package:

```
fixmodel_bin(data = trial_data, arm = 3, alpha = 0.025)
```

Input:

- Data frame with trial data
- Arm to perform inference on
- Significance level

treatment	period	response
0	1	0
1	1	1
0	1	1
...	...	...

Modelling approaches – Frequentist model-based approach

Implementation in the NCC package:

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fixmodel_bin(data = trial_data, arm = 3, alpha = 0.025)
```

Input:

- Data frame with trial data
- Arm to perform inference on
- Significance level

treatment	period	response
0	1	0
1	1	1
0	1	1
...	...	...

Output:

- One-sided p-value
- Estimated treatment effect in terms of the log-odds ratio
- 95% confidence interval for the log-odds ratio
- Indicator of whether the null hypothesis was rejected or not
- Fitted model

Analogous function for continuous endpoints:

```
fixmodel_cont(data = trial_data, arm = 3, alpha = 0.025)
```

Modelling approaches – Bayesian Time Machine

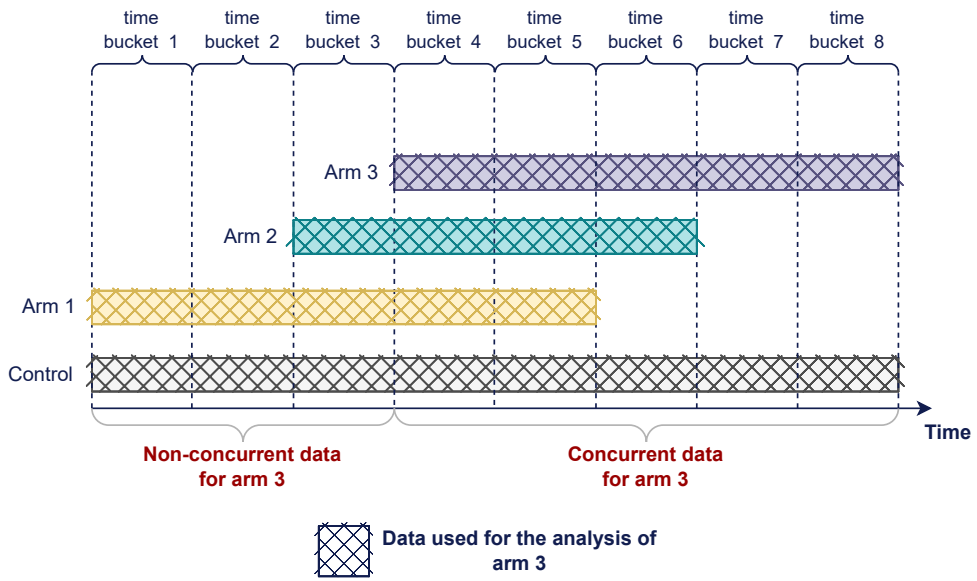
Divides the trial duration into time buckets indexed by c and smooths the control response over time using a second-order Bayesian normal dynamic linear model[2]:

$$g(E(y_j)) = \eta_0 + \theta_{k_j} + \alpha_{c_j}$$

where α_{c_j} models the drift over time, considering $\alpha_1 = 0$ and

$$\alpha_2 \sim \mathcal{N}(0, 1/\tau) \quad \text{and} \quad \alpha_c \sim \mathcal{N}(2\alpha_{c-1} - \alpha_{c-2}, 1/\tau)$$

- Normal priors on the control response and treatment effects
- Gamma prior on τ
- Closer time buckets are assumed to be more similar



[2] Saville, B. R., Berry, D. A., et al. (2022). The Bayesian Time Machine: Accounting for Temporal Drift in Multi-arm Platform Trials. Clinical Trials.

Modelling approaches – Bayesian Time Machine

Implementation in the NCC package:

```
timemachine_bin(data = trial_data, arm = 3, alpha = 0.025,
                bucket_size = 25, prec_theta = 0.001, prec_eta = 0.001,
                tau_a = 0.1, tau_b = 0.01)
```

Input:

- Data frame with trial data
- Arm to perform inference on
- Decision boundary
- Bucket size
- Parameters for prior distributions

treatment	period	response
0	1	0
1	1	1
0	1	1
...	...	...

Modelling approaches – Bayesian Time Machine

Implementation in the NCC package:

```
timemachine_bin(data = trial_data, arm = 3, alpha = 0.025,
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                tau_a = 0.1, tau_b = 0.01)
```

Input:

- Data frame with trial data
- Arm to perform inference on
- Decision boundary
- Bucket size
- Parameters for prior distributions

treatment	period	response
0	1	0
1	1	1
0	1	1
...	...	...

Output:

- Posterior probability that the log-odds ratio is less than zero
- Estimated treatment effect in terms of the posterior mean of log-odds ratio
- 95% credible interval for the log-odds ratio
- Indicator of whether the null hypothesis was rejected or not

Analogous function for continuous endpoints:

```
timemachine_cont(data = trial_data, arm = 3, alpha = 0.025, ...)
```

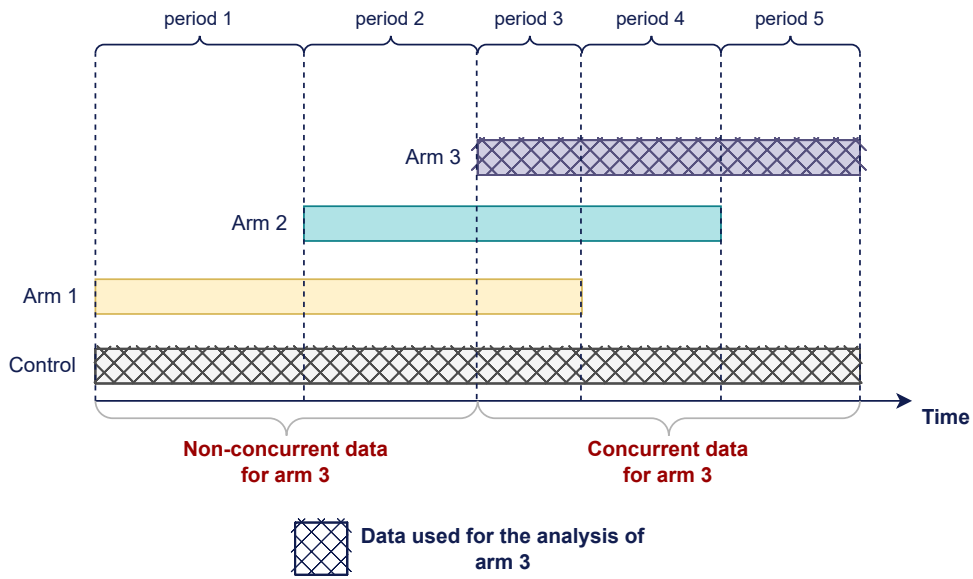
Downweighting approaches – Meta-analytic-predictive (MAP) prior approach

Derives a prior distribution for the control response in the concurrent periods from the non-concurrent control data[3].

MAP prior: $p_{MAP}(\eta_{CC})$ for the concurrent control response derived as a posterior distribution of the response in the NCC data

Robustified MAP: Mixture of the MAP prior and a non-informative prior

- Normal prior on the control response in non-concurrent periods
- The MAP approach takes into account the heterogeneity of the control data from different periods to decide the amount of borrowing



[3] Schmidli, H., et al. (2014). Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics.

Downweighting approaches – MAP prior approach

Implementation in the NCC package:

```
MAPprior_bin(data = trial_data, arm = 3, alpha = 0.025,
             prior_prec_tau = 4, prior_prec_eta = 0.001,
             robustify = TRUE, weight = 0.1)
```

Input:

- Data frame with trial data
- Arm to perform inference on
- Decision boundary
- Parameters for prior distributions
- Weight for the non-informative prior component in the robustified MAP

treatment	period	response
0	1	0
1	1	1
0	1	1
...	...	...

Downweighting approaches – MAP prior approach

Implementation in the NCC package:

```
MAPprior_bin(data = trial_data, arm = 3, alpha = 0.025,
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             robustify = TRUE, weight = 0.1)
```

Input:

- Data frame with trial data
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treatment	period	response
0	1	0
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0	1	1
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Output:

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- 95% credible interval for the log-odds ratio
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Analogous function for continuous endpoints:

```
MAPprior_cont(data = trial_data, arm = 3, alpha = 0.025, ...)
```

How to run a simulation study using the NCC package

- A set of scenarios is analyzed using indicated models
- Inference is performed for given treatment arms
- Probability to reject H_0, bias and mean squared error of the treatment effect are simulated based on a given number of replications

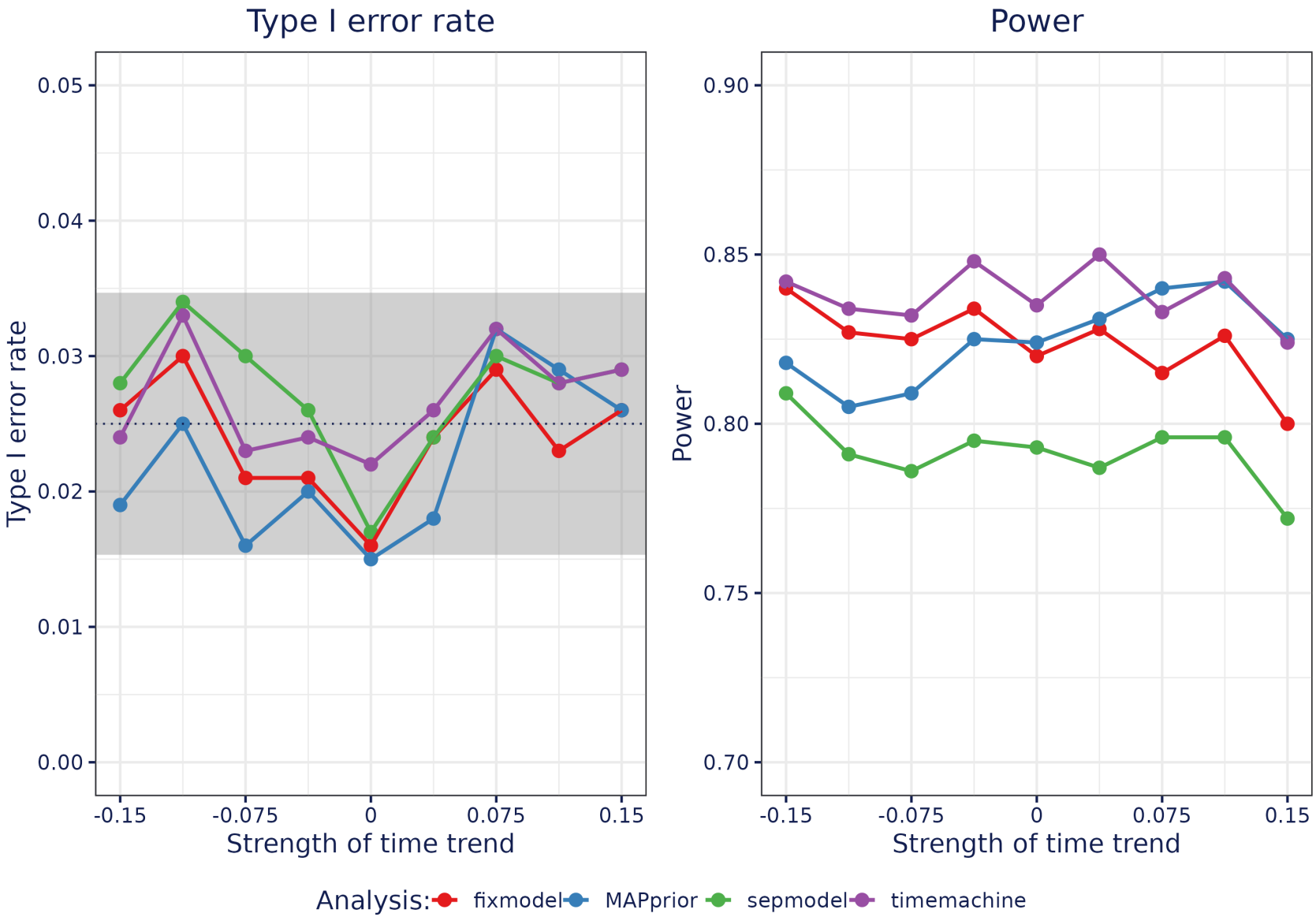
`sim_scenarios:`

num_arms	n_arm	d1	d2	d3	p0	OR1	OR2	OR3	lambda0	lambda1	lambda2	lambda3	trend
3	250	0	250	500	0.5	1	1	1	-0.15	-0.15	-0.15	-0.15	linear
3	250	0	250	500	0.5	1	1	1	0	0	0	0	linear
3	250	0	250	500	0.5	1	1	1	0.15	0.15	0.15	0.15	linear
...	...	...	...	...	...	...	...	...	...	...	...	...	...

Performing simulations for a given set of scenarios

```
sim_study_par(nsim = 1000, scenarios = sim_scenarios, arms = 3,
              models = c("fixmodel","timemachine","MAPprior","sepmodel"),
              endpoint = "bin")
```

Results of the simulation study



Conclusions

The NCC R-package

- Enables **simulation of platform trials** with continuous or binary endpoints under a wide range of scenarios
- Provides the **implementation of analysis methods** for incorporating NCC
- Allows to evaluate the properties and robustness of the implemented methods in **simulation studies**
- Is available on CRAN and comes with an **accompanying website**: `https://pavlakrotka.github.io/NCC/`

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Ongoing work

- **Alternative models** for incorporating non-concurrent controls
  - Mixed effect models, spline regression
- Further improvements in the package **documentation** and **website**

Selected references

- Krotka, P., Hees, K., et al. *"NCC: An R-package for analysis and simulation of platform trials with non-concurrent controls."* arXiv:2302.12634 (2023).
- Bofill Roig, M., Krotka, P., et al. *"On model-based time trend adjustments in platform trials with non-concurrent controls."* BMC Medical Research Methodology (2022).
- Saville, B. R., Berry, D. A., et al. *"The Bayesian Time Machine: Accounting for Temporal Drift in Multi-arm Platform Trials."* Clinical Trials (2022).
- Schmidli, H., Gsteiger, S., et al. *"Robust meta-analytic-predictive priors in clinical trials with historical control information."* Biometrics (2014).
- Weber, S., Li, Y., et al. *"Applying Meta-Analytic-Predictive Priors with the R Bayesian Evidence Synthesis Tools."* Journal of Statistical Software (2021).

Thank you for your attention!

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