Bayesian optimization of protocols for neurostimulation

Lorenz Wernisch

BIOS Health Ltd

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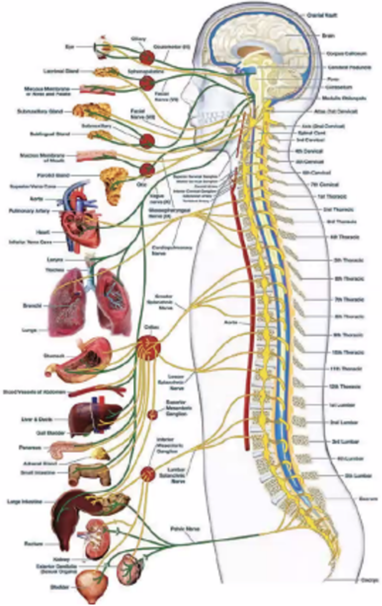
Bioelectronic therapies

Organs are controlled and regulated by peripheral nervous system

Traditional **biochemical** interventions

Bioelectronic medicines leverage nervous system directly with highly specific, fast and dynamic interventions



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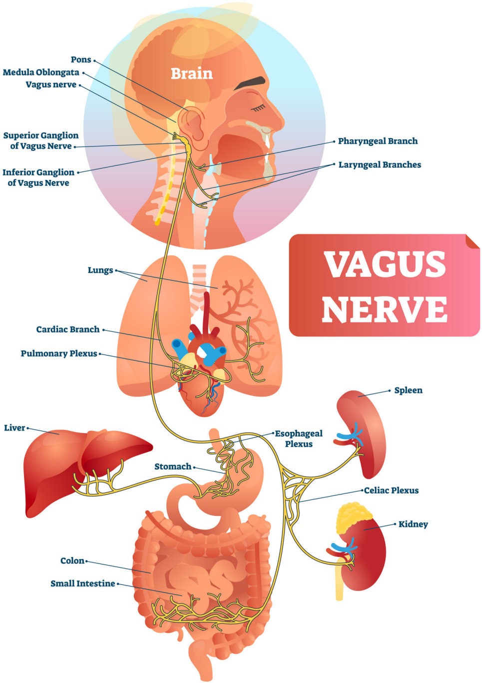
Vagus nerve

Part of **parasympathetic (calming)** nervous system

Two way traffic:

Afferent messages from organs to brain

Efferent messages from brain to organs



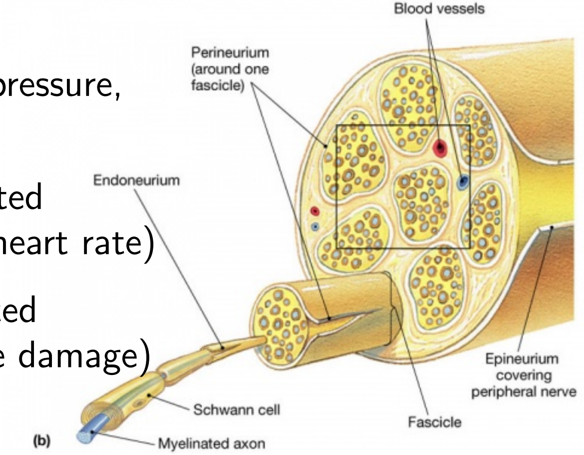
Cross section of a nerve

Hierarchical organisation into fascicles, types of fibres:

A: large, myelinated
fast (eg sense lung pressure, blood pressure)

B: medium, myelinated
slower (eg regulate heart rate)

C: small, unmyelinated
slow (eg sense tissue damage)



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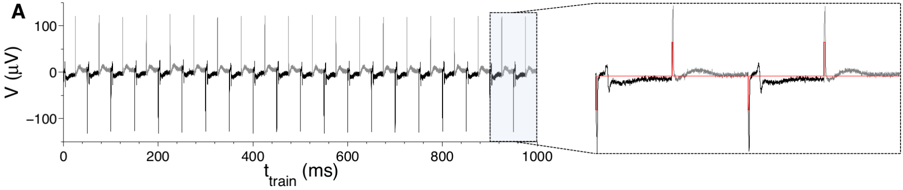
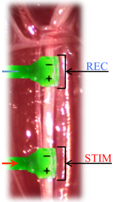
Stimulation by electric pulses



Train of alternating-monophasic stimulation

M Ward et al, A Flexible Platform for Biofeedback-driven Control and Personalization of Electrical Nerve Stimulation, Therapy, 2015



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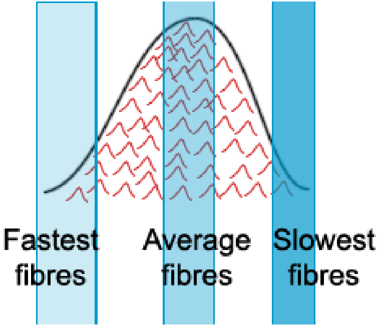
Nerve response to stimulation



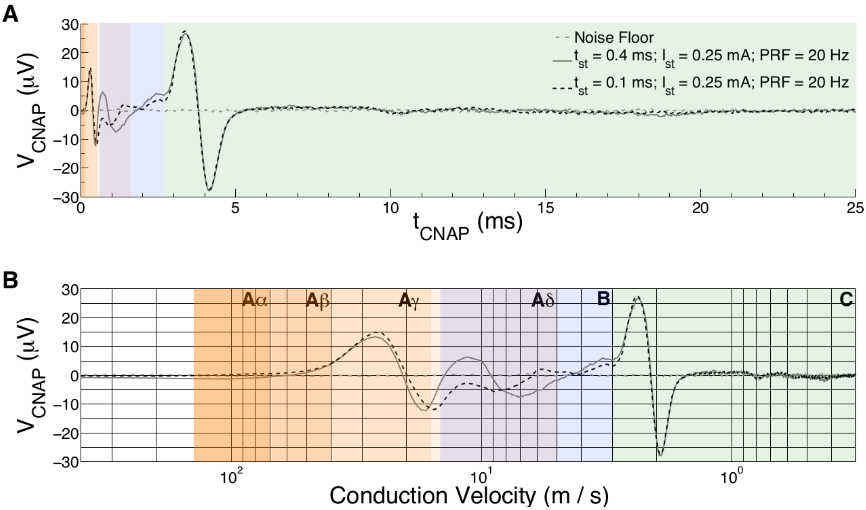
Individual nerve cells triggered by **stimulation** electrodes

Action potentials travel at (slightly) different speeds

Response recorded by **recording** electrodes

Artificial responses affect organs similar to natural ones

Velocity chart for fibre types



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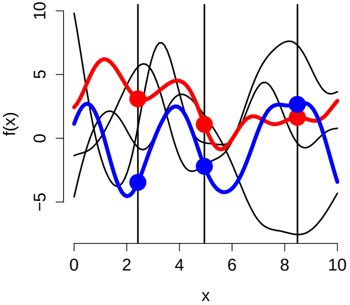
Gaussian process prior



Family of functions via covariance K on input points x

$y \sim N(0, K_{xx})$

Prediction for x^* from (x, y)

$y^* \sim N(K_{x^*x}K_{xx}^{-1}y, \Sigma)$

$\Sigma = K_{x^*x^*} - K_{x^*x}K_{xx}^{-1}K_{xx^*}$

Gaussian kernel $\mathrm{cov}(x, x^*) = \theta_1 \exp(-\theta_2(x - x^*)^2)$

Power from flexibility in kernel design and combinations

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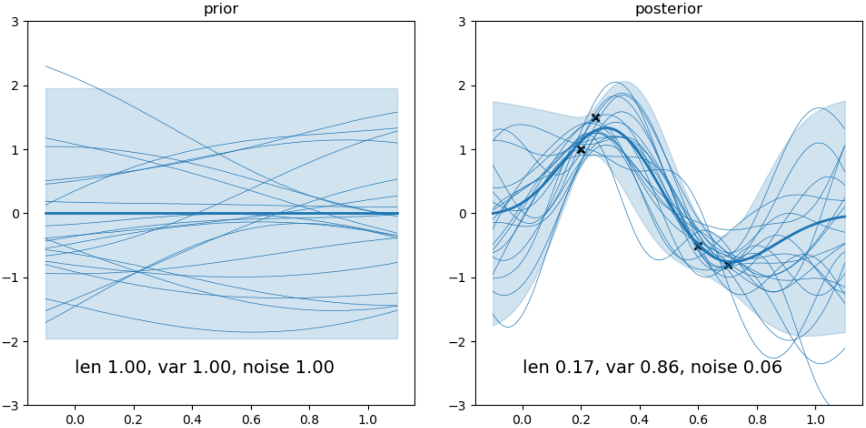
GP posterior uncertainty and samples



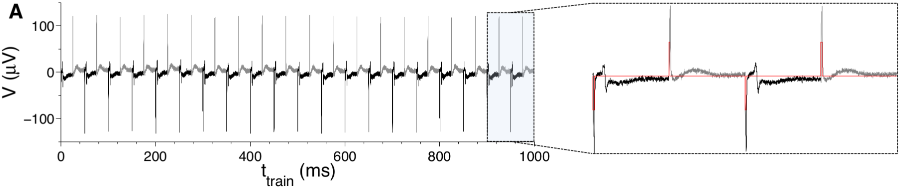
Estimate GP parameters by maximum likelihood

Vagus nerve stimulation in rats

M Ward et al, A Flexible Platform for Biofeedback-driven Control and Personalization of Electrical Nerve Stimulation, Therapy, 2015

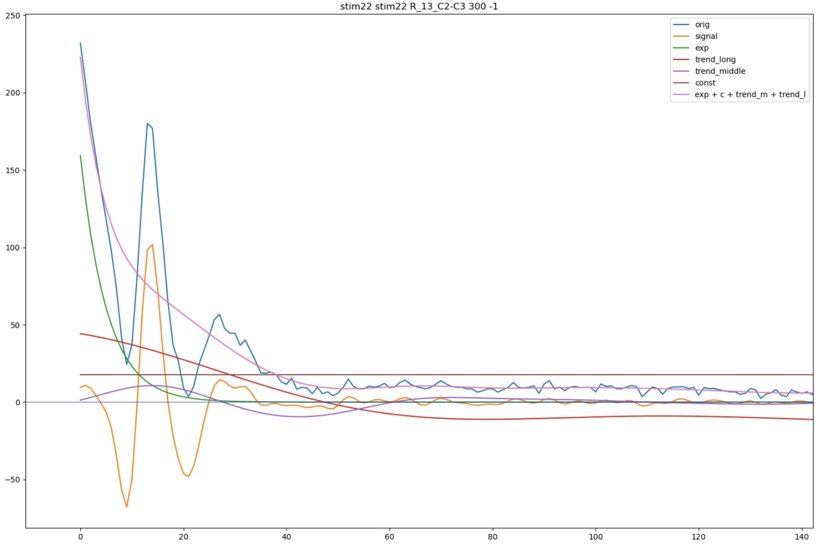
- Trials with 12 subjects
- Left cervical branch of vagus nerve
- 7 pulse currents 0, 0.2,..., 1.2
- 4 pulse durations 0.1, 0.2, 0.4, 0.8, for 20 secs
- Alternating monophasic, 10Hz, for 1 second
- Responses recorded

Stimulation by electric pulses



1s train of alternating-monophasic stimulation, 10Hz

Response decomposition by GP



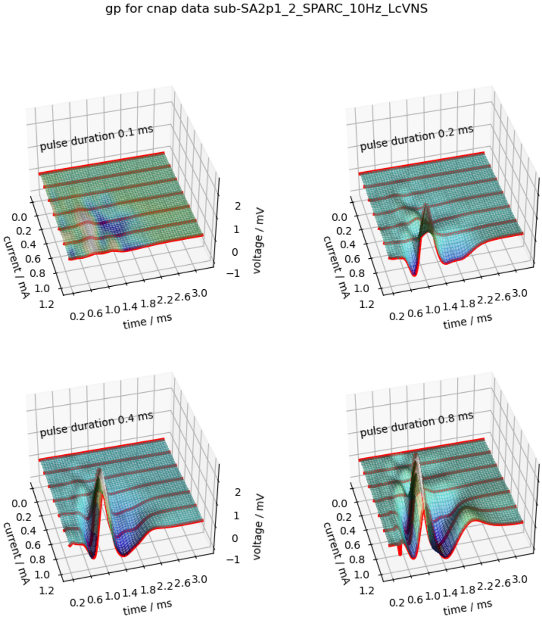
Kernels: exponential decay, trends, signal, noise

Modelling nerve responses by GPs

Stimulation:
pulse duration,
current

Response:
time series

GP model:
Input:
curr x dur x time
Ouput:
voltage



Finding optimal stimulation parameters

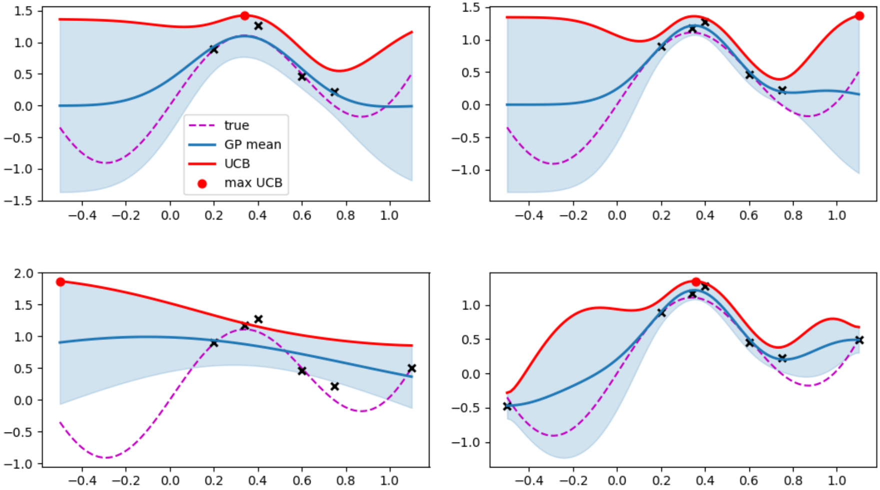
- Maximise overall nerve or physiologial response
- Minimize distance of response to target setpoint
- Need to adjust stimulation parameters to changes
- Exploit previous trials or data

Bayesian optimization

Bayesian optimization

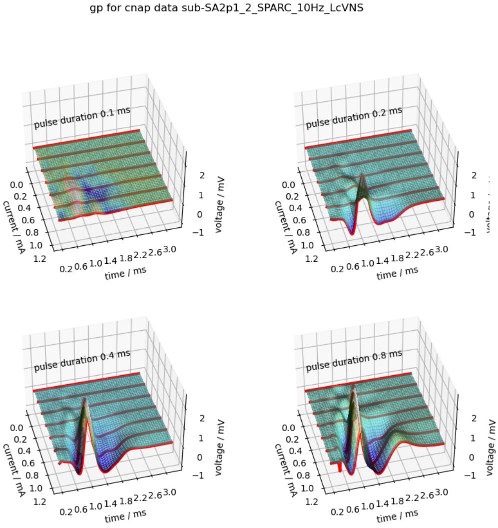
- Optimize unknown function: evaluation at given test points
- Model current function by GP
- Use current GP mean and variance to find new test point:
  - to reduce uncertainty about true function
  - to optimize function
- Iterate until stopping criterion met (eg little change in optimum, enough reduction in uncertainty)

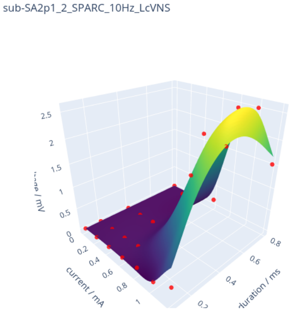
Bayesian optimization



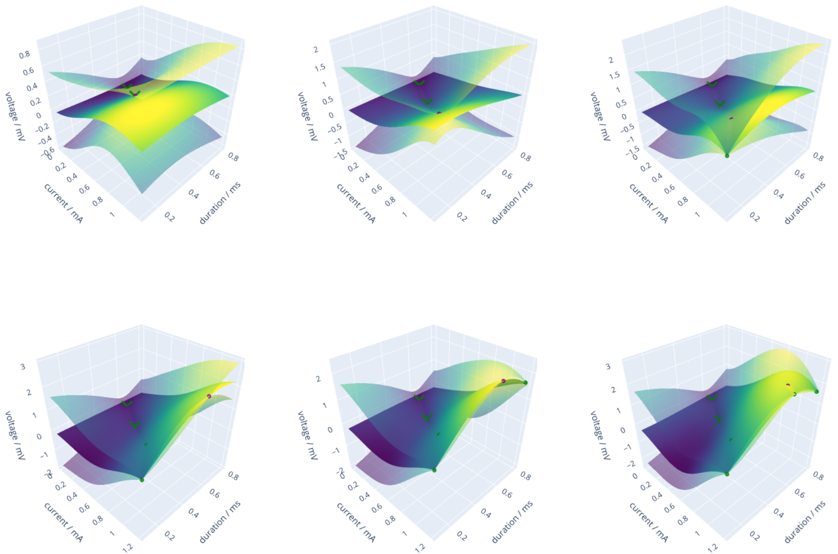
Upper Confidence Bound or Expected Improvement

Bayesian optimization of max response



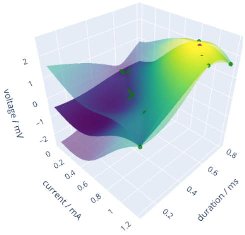


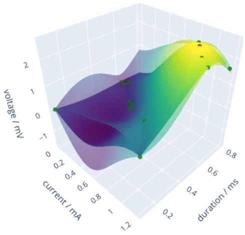
Build GP simulator from max nerve response in trial

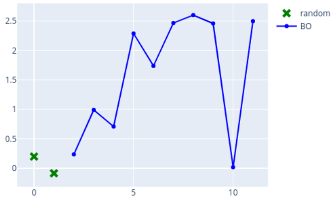


voltage / mV
current / mA
duration / ms

BO of max nerve response







Typically acceptable maximum reached in less than a dozen of steps

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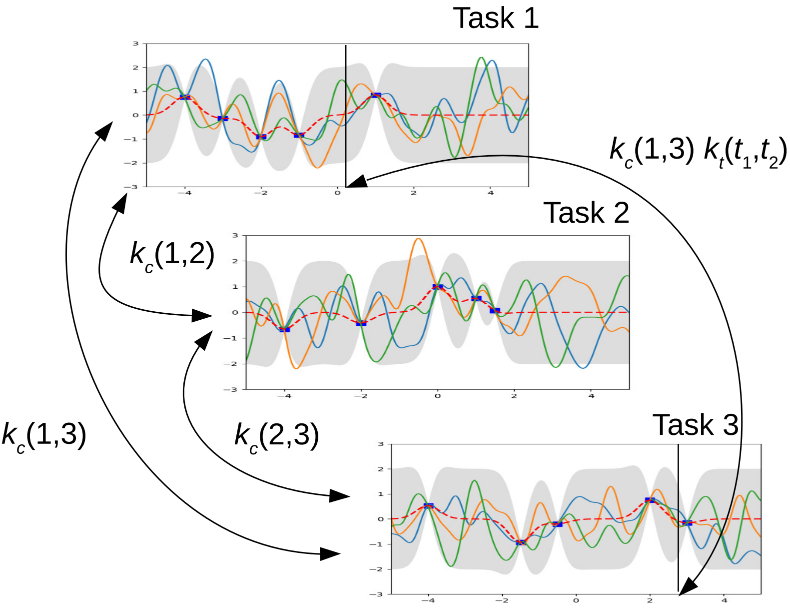
Joint GP for multiple trials?

Update with consecutive data points from the same trial works fine

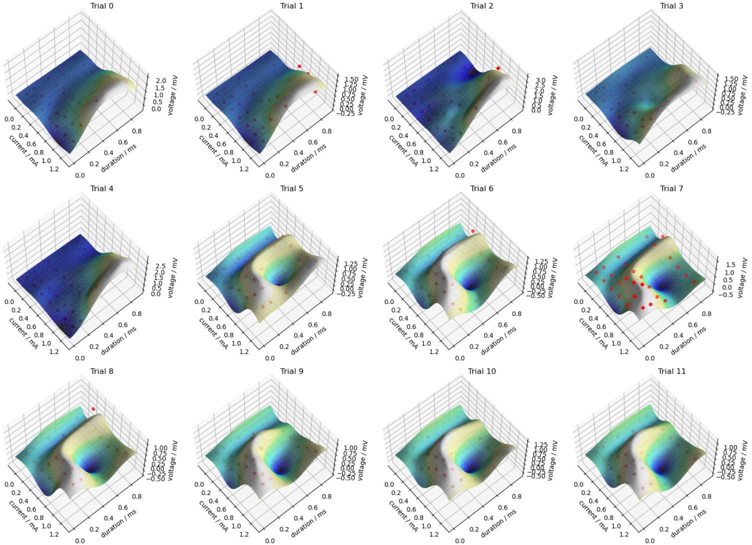
Increased stability and efficiency of BO from multiple trials as priors?

Use multitask GP

Multitask GP



Maximum nerve response trials



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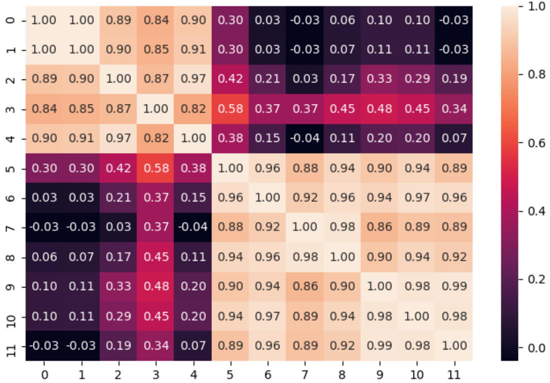
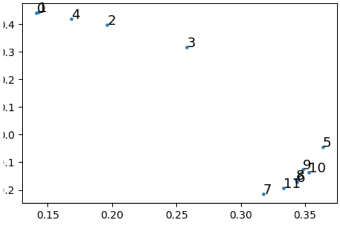
Coregionalisation kernel of multitask GP





GP estimation of kernel by Cholesky parametrization

PC 1 and 2 of Eigendecomposition of kernel

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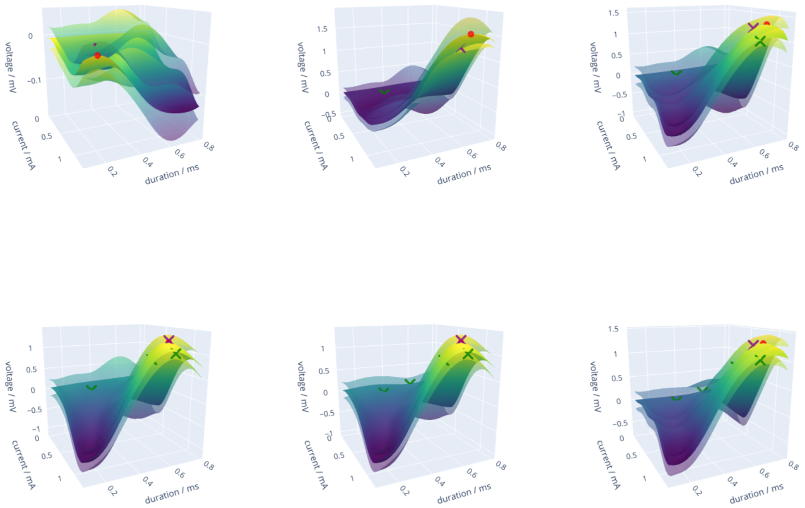
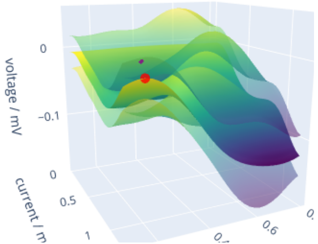
Bayesian optimization with priors

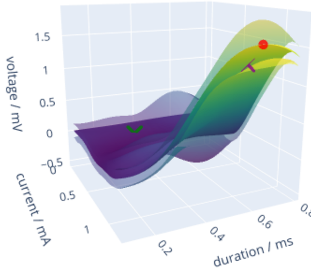
- Select suitable prior trials
- Extend kernel to new trial
- No need even for initial query points, prior trials typically suggest good starting points

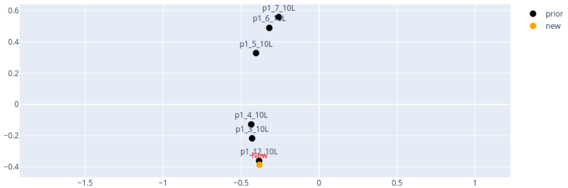
Demo: select 6 previous trials


voltage / mV
current / mA
duration / ms

BO with prior







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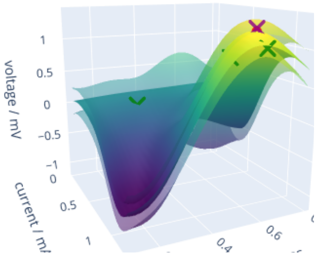
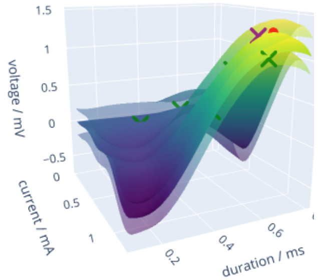
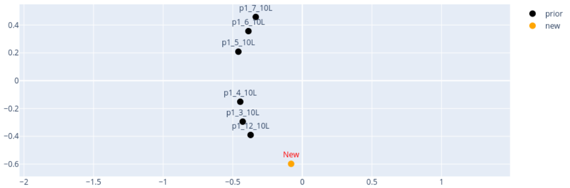
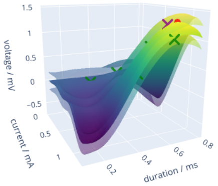
BO with prior

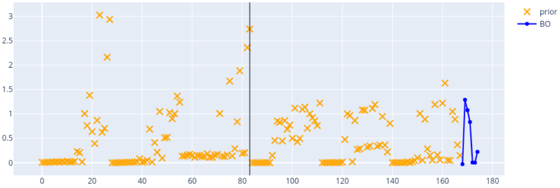






BO of max nerve response

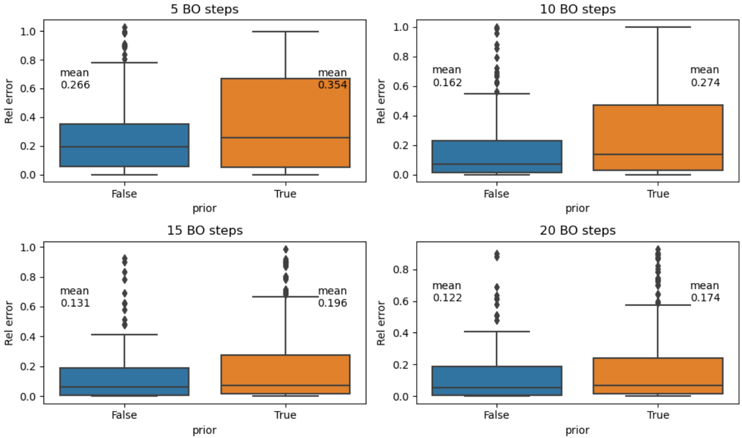




Systematic test of BO with prior

- Obtain true maximum of simulator
- Simulator provides noisy data for BO and BO with prior
- Evalute maximum input suggested by BOs on simulator
- Compare how close to true maximum
- Variables:
  - noise-signal ratio NSR
  - number of priors
  - number of queries

Relative error with unweighted BO priors



Compared to BO without prior BO with prior performs worse particularly for small numbers of BO queries

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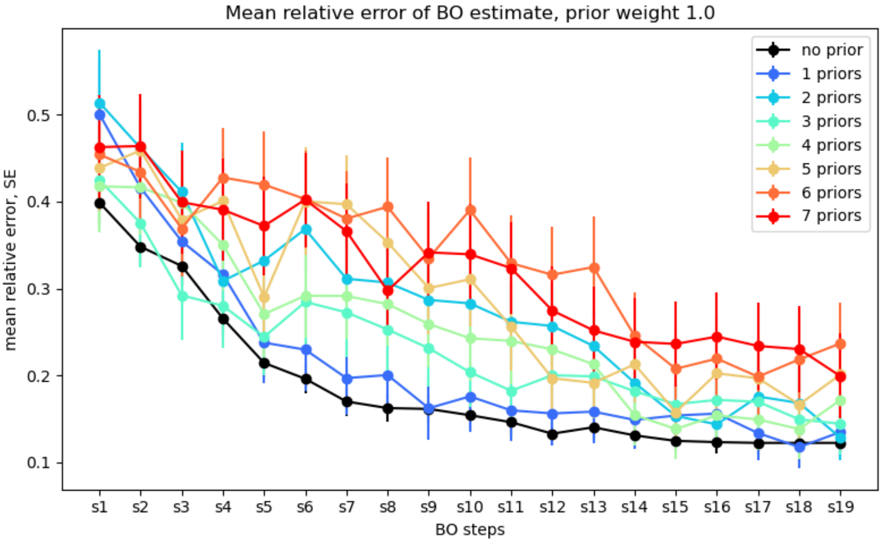
Relative error with unweighted BO priors



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Weighted likelihood

$f \sim N(0, K_{xx})$, $(y - f)|f \sim N(0, \sigma^2 I)$

Points weighted by $W = \text{diag}\,(w_1, \ldots, w_n)$
results in likelihood term $(y - f)^T W (y - f)/\sigma^2$

$\text{cov}(y) = K_{xx} + \sigma^2 I$ to $\text{cov}(y) = K_{xx} + \sigma^2 W^{-1}$

Equivalently, rescale kernels and data:

$$f^* = K_{x^* x}(K_{xx} + \sigma^2 W^{-1})^{-1} y = \tilde{K}_{x^* x}(\tilde{K}_{xx} + \sigma^2 I)^{-1} \tilde{y}$$

$$\tilde{K}_{x^* x} = K_{x^* x} W^{1/2},\ \tilde{K}_{xx} = W^{1/2} K_{xx} W^{1/2},\ \tilde{y} = W^{1/2} y$$

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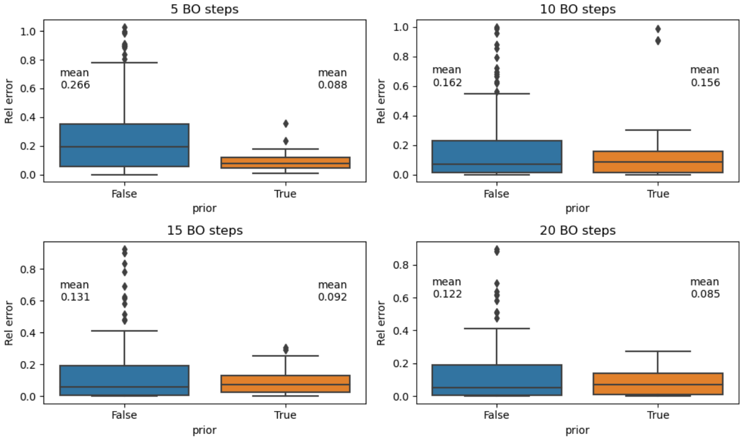
Relative error with weighted BO priors



Excellent performance of BO with weighted priors (0.1) and many prior trials (7) for few steps

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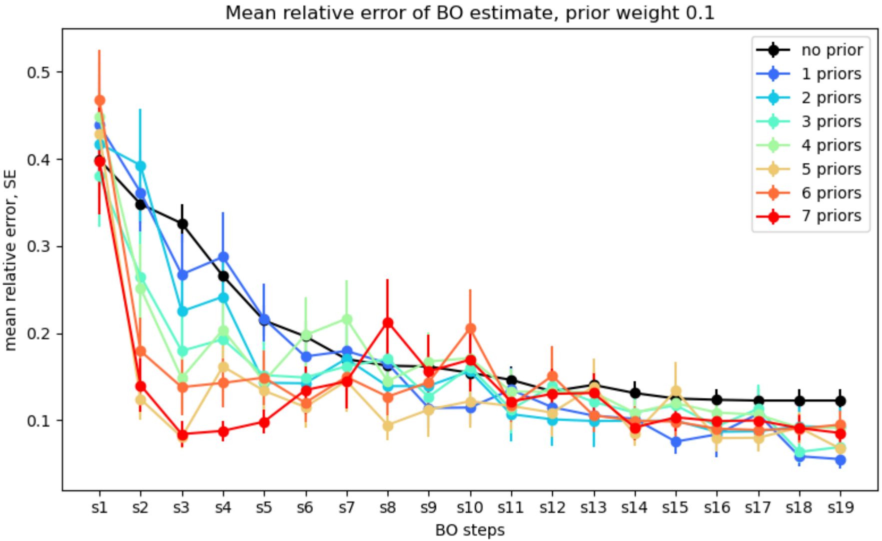
Relative error with weighted BO priors



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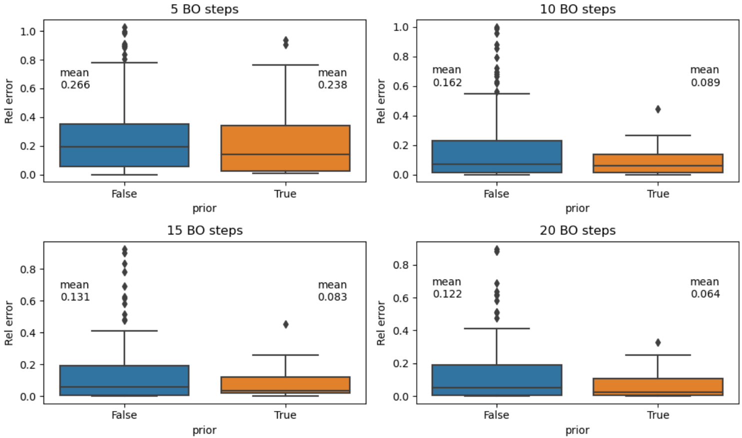
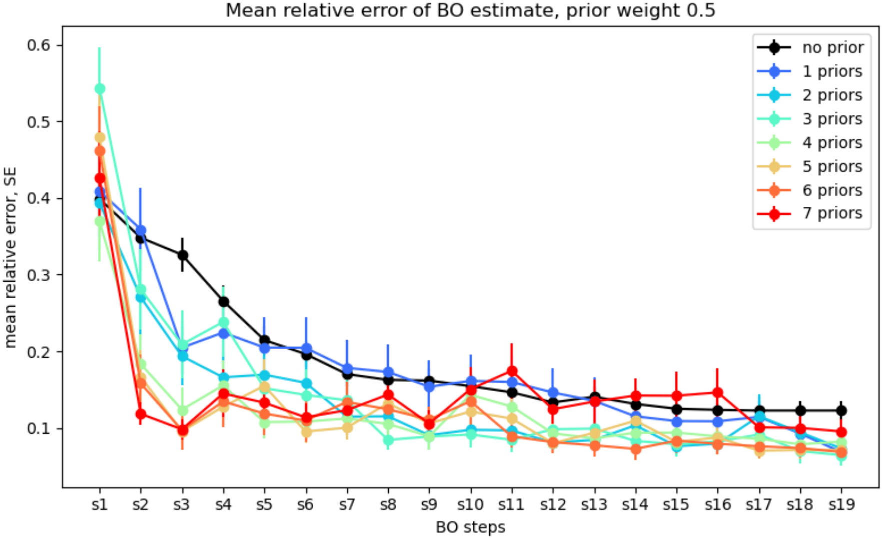
Relative error with weighted BO priors



Excellent performance of BO with weighted priors (0.5) and fewer prior trials (3) for more steps

Relative error with weighted BO priors



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Final thoughts

- Bioelectronic treatments are highly dynamic and time critical compared to traditional therapies
- Full stack solutions required: surgery, electronics, data management, algorithms tightly interlinked
- Bayesian approaches provide stability and robustness through controlled regularisation
- Theoretical considerations of statistical and ML methods directly inspired by practical experience

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We are recruiting

If you are interested in working in this kind of environment, get in touch:

https://www.bios.health/careers

careers@bios.health

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