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**Sample-size estimation**

* You should state whether an appropriate sample size was computed when the study was being designed
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* If no explicit power analysis was used, you should describe how you decided what sample (replicate) size (number) to use

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We did not perform any sample-size estimation in this numerical study.

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* You should include a definition of biological versus technical replication
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* High-throughput sequence data should be uploaded before submission, with a private link for reviewers provided (these are available from both GEO and ArrayExpress)

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* Statistical analysis methods should be described and justified
* Raw data should be presented in figures whenever informative to do so (typically when N per group is less than 10)
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We wrote in each figure legend which summary statistics are used

**Group allocation**

* Indicate how samples were allocated into experimental groups (in the case of clinical studies, please specify allocation to treatment method); if randomization was used, please also state if restricted randomization was applied
* Indicate if masking was used during group allocation, data collection and/or data analysis

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**Additional data files (“source data”)**

We have no group allocation

* We encourage you to upload relevant additional data files, such as numerical data that are represented as a graph in a figure, or as a summary table
* Where provided, these should be in the most useful format, and they can be uploaded as “Source data” files linked to a main figure or table
* Include model definition files including the full list of parameters used
* Include code used for data analysis (e.g., R, MatLab)
* Avoid stating that data files are “available upon request”

Please indicate the figures or tables for which source data files have been provided:

We provided the source data (simulated time traces with instrumental noise) for Fig. 1, 2 , 3, 4, 7, 10, 11, 12 which were also used in Fig 5,6 though with different instrumental noise settings. The data used in Fig. 8,9 is identical to the data used in 7.

Box 1 Fig 1 sketches how in principle the algorithm works and which statistical problem of macroscopic data of a linear first order Markov process we try to account for. Thus we did not include source data files for this plot. Instead we show in Box 1 Fig 2 that the mentioned statistical problem is indeed present for the previous gold standard algorithm by using the source data of Fig. 4 with 4000 ion channel per patch but any other data set would serve for that purpose.