A hybrid population model enables the study of single-cell heterogeneity in an epigenetic memory system.

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Single-cells measurement techniques like flow cytometry allow heterogeneity in biological systems to be quantified efficiently. However, many modelling approaches currently cannot capture this behavior, as often only an average cell is covered in commonly used ODE models [2]. Single-cell data can of course be reduced to its mean to be usable with these models, but this leads to a loss of information in the data and, more importantly, is only an accurate description if the data is close to a normal distribution. Especially in the case of bimodal distributions, which can for example occur in bistable systems, averages are poor descriptions of the data and lack the ability to reproduce important features of the system (Fig. 1).

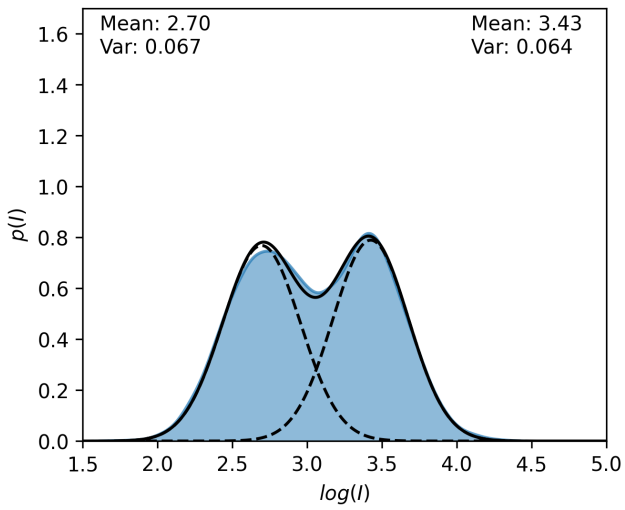

Figure 1: Exemplary experimental data. Blue area shows the kernel density estimation for flow cytometry measurements with a Gaussian mixture model fit in black.

The synthetic epigenetic memory system from Maier *et al.* [3] and Graf *et al.* [1] is such a particular system. It is characterized by the ability to switch from an OFF- to an ON-state through a transient metabolic trigger. This ON-state is

sustained via positive feedback based on DNA methylation. A large part of the cells can remember this state for many days, but eventually, more and more cells switch back to the OFF-state. In the experimental data, this is observable as two subpopulations, ON- and OFF-cells. We aim to capture this bimodality by a tailored model which describes heterogeneous single-cell trajectories. While many stochastic modeling approaches exist for similar problems, we choose a hybrid model here. This model combines the simulation speed of differential equations with a stochastic process describing cell division, as well as distributed parameters (Fig. 2). The simulated population is then compared to the data using Gaussian mixture models (also seen in Fig. 1). We show that the model is able to reproduce experimental single-cell data and, in addition, gives insights into mechanisms for the ON to OFF switch in individual cells.

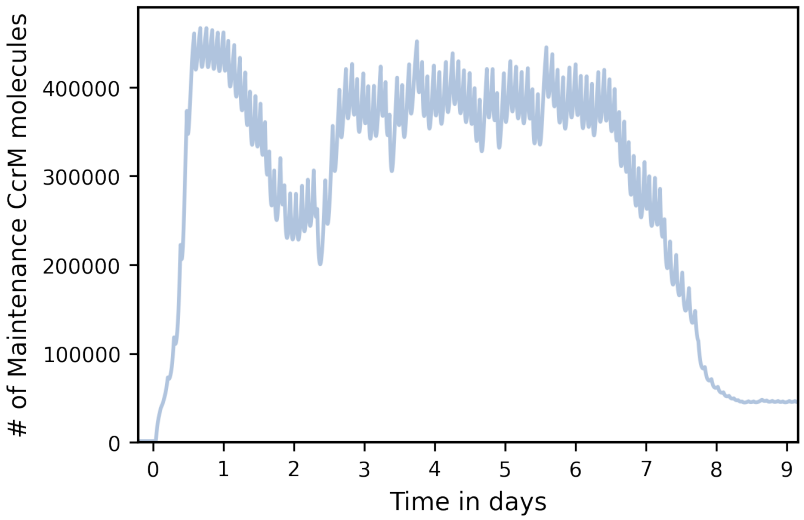

Figure 2: Single cell trajectory. The blue curve represents one simulation with a stochastic process for the cell division.

References

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3. Maier, J., Möhrle, R. & Jeltsch, A. Design of synthetic epigenetic circuits featuring memory effects and reversible switching based on DNA methylation. *Nat Commun* **8** (2017).