Supplementary Materials: Accounting for Randomness in Measurement and Sampling in Studying of Cancer Cell Population Dynamics

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Section A: Flow cytometric analysis of HROC87

Flow cytometric analysis of HROC87, a cell line recently established from a primary colorectal cancer [1]. Exemplary data from 1 of 50 (S1) measurements and from 1 of 100 (S2) measurements are given. Similar data have also been generated from another cell line: HROC113 (data not shown). Of note, the analysis was performed in very low passages of the cell line.

The cells were harvested from cell culture in the exponential growth phase (approximately 80% density), washed with phosphate-buffered saline and incubated with 5µM Vybrant®Dye Cycle™ Violet Stain (VDC; Life Technologies, Frankfurt, Germany) in hanks-balanced salt solution for 30min at 37°C in the dark. In the control measurements (S1), 50µM Verapamil (Sigma-Aldrich, Hamburg, Germany) was added before the addition of VDC to block the dye-efflux by membrane-bound pumps. Cells were kept at 37°C until analysis for a maximum of 3 hours. Propidium iodide (1µg/ml; Life Technologies) was added shortly before measurement to allow for life/dead cell discrimination.

Samples were analyzed on a FACS ARIA II cell sorter equipped with standard lasers using the Diva software package (both from Becton Dickinson, Heidelberg, Germany). 100.000 events (all dots in S1(a) and S2(a) were counted per measurement.

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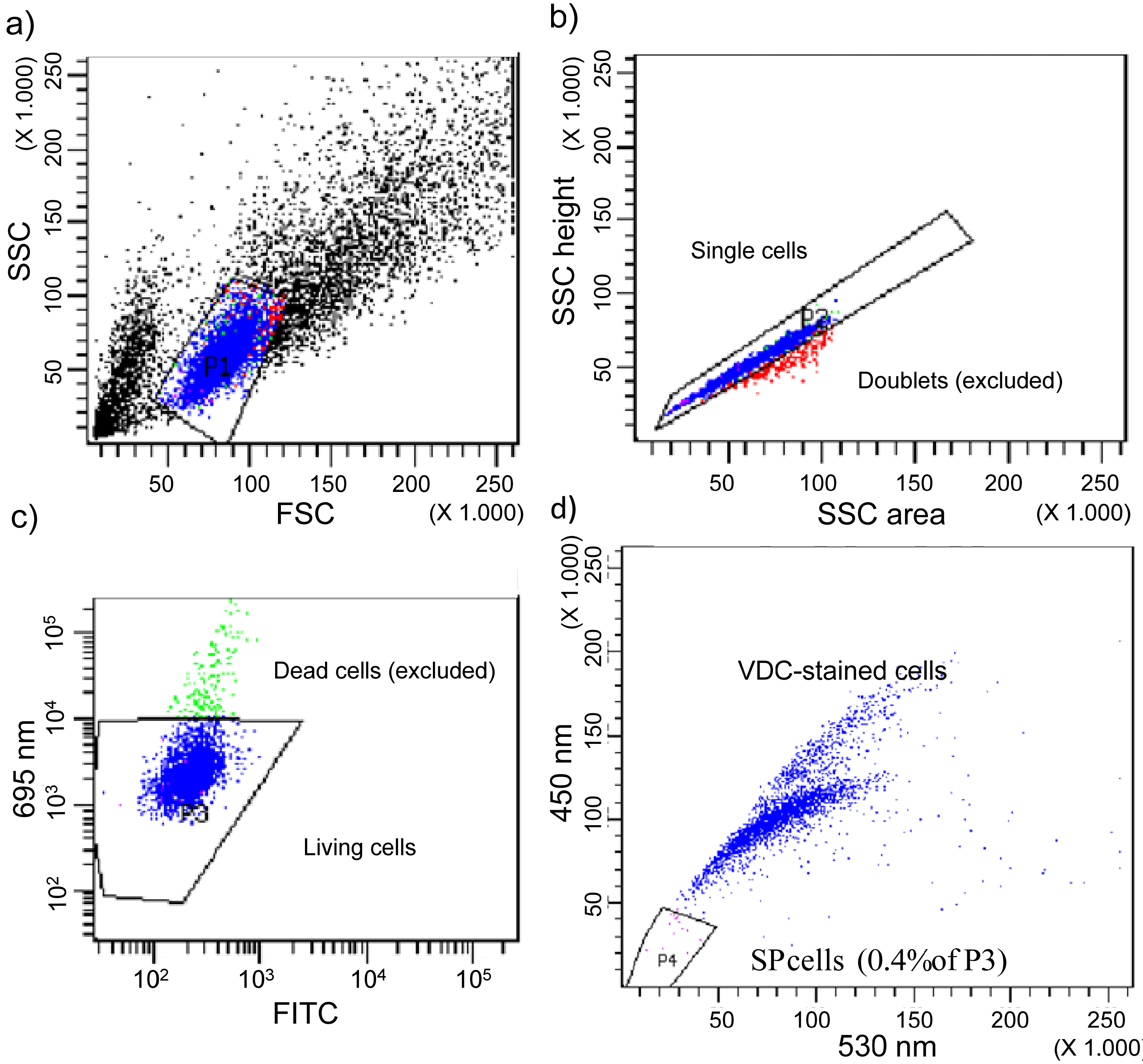

Fig. S1. Exemplary data from 1 of 50 measurements a) Cell size and granularity b) Exclusion of doublets c) Exclusion of dead cells P_3 d) SP Determination.

The gating strategy was as follows. S1(a) and S2(a): gate P1 was set in the forward scatter (FSC; cell size;X-axis) / sideward scatter (SSC; cell granularity;Y-axis) blot on the main cell population (blue dots). S1(b) and S2(b): In the SSC-area (X-axis) versus SSC-height blot (Y-axis), gate P2 was set to exclude doublets (red dots). S1(c) and S2(c): Dead cells were excluded by gating on the PI negative cells measured in the 695 channel (Y-axis; P3; green dots). For a better display, the blots additionally give the empty Fluorescein isothiocyanate (FITC) channel (X-axis). S1(d) and S2(d). Finally, the events were displayed in the 530 nm channel (X-axis) versus the V450 channel (Y-axis). The side population (SP) cells are those able to pump the VDC stain out of their cytoplasm (pink dots). They are not positively stained for VDC and lie within gate P4. Percentages of cells within P4 are given for the control cells (incubated with Verapamil and VDC; S1 and for the SP cell analysis (incubated with VDC but without inhibitor; S2.)

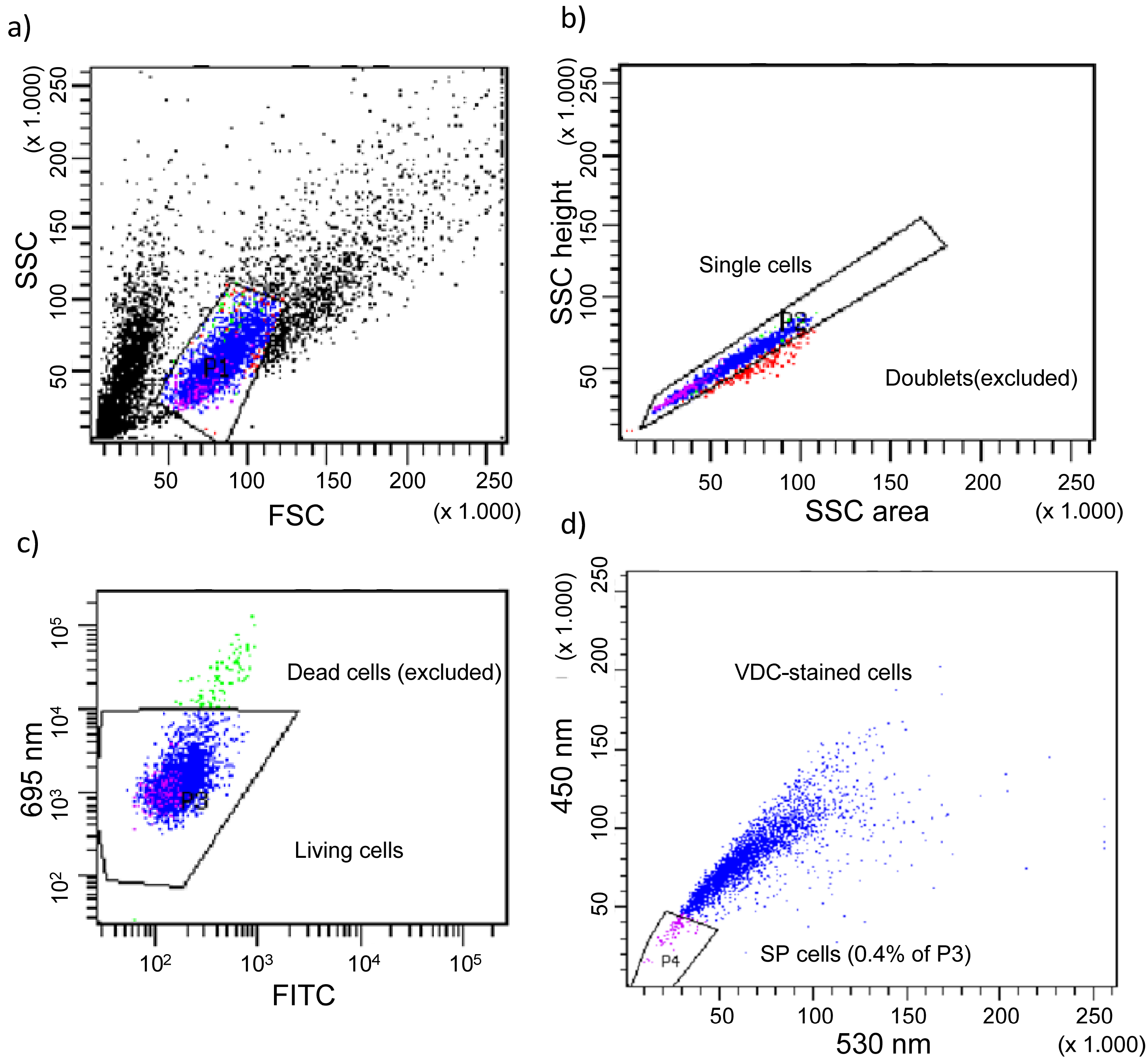

Fig. S2. Exemplary data from 1 of 100 measurements a) Cell size and granularity b) Exclusion of doublets c) Exclusion of dead cells P_3 d) SP Determination.

Section B. Proof of Theorem 1

The observation model for cell division process in each sample is given by

$$2\begin{bmatrix} \tilde{v}_{1,i}^{(0)} & \tilde{v}_{2,i}^{(0)} & \cdots & \tilde{v}_{M,i}^{(0)} \\ \tilde{v}_{1,i}^{(1)} & \tilde{v}_{2,i}^{(1)} & \cdots & \tilde{v}_{M,i}^{(1)} \\ \vdots & \vdots & \ddots & \vdots \\ \tilde{v}_{1,i}^{(NMS-2)} & \tilde{v}_{2,i}^{(NMS-2)} & \cdots & \tilde{v}_{M,i}^{(NMS-2)} \end{bmatrix} \begin{bmatrix} p_{1l} \\ p_{2l} \\ \vdots \\ p_{Ml} \end{bmatrix} + \begin{bmatrix} \eta_{l,i}^{(1)} \\ \eta_{l,i}^{(2)} \\ \vdots \\ \eta_{l,i}^{(NMS-1)} \end{bmatrix} = \begin{bmatrix} v_{l,i}^{(1)} \\ v_{l,i}^{(2)} \\ \vdots \\ v_{l,i}^{(NMS-1)} \end{bmatrix} \tag{S1}$$

where, $i \in \{1, N\}$. The equation (S1) is satisfied for each sample, i, and cell type, l. The goal is to find p_{hl}, $h, l \in [1, M]$, which fit the equations best in the minimum mean squared sense. We have

$$\hat{\mathbf{P}} = \arg\min_{\mathbf{P}} S(\mathbf{P}) \tag{S2-a}$$

$$\text{s.t.}$$

$$\text{for } \forall \ \ 1 \le h \le M, 1 \le l \le M,$$

$$0 \le p_{hl} \le 1, \tag{S2-b}$$

$$\sum_{l=1}^{M} p_{hl} = 1, \tag{S2-c}$$

where the objective function S is defined as

$$S(\mathbf{P}) = \sum_{l=1}^{M} \sum_{i=1}^{N} \sum_{j=1}^{NMS-1} \left(v_{l,i}^{(j)} - 2\sum_{h=1}^{M} \tilde{v}_{h,i}^{(j-1)} p_{hl} \right)^2, \tag{S3}$$

The optimization problem in (S2) is convex, (cost function is quadratic and constraints are linear [2]). Using KKT (Karush–Kuhn–Tucker), the unconstrained solution for this problem is given by

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$$S_U(\mathbf{P}) = \sum_{l=1}^{M} \left(S(\mathbf{P}_l) + \lambda_l \left(\sum_{h=1}^{M} p_{hl} - 1 \right) + \sum_{h=1}^{M} (\lambda'_{hl} - \lambda''_{hl}) p_{hl}, \right) \tag{S4}$$

where λ'_{jl}, λ''_{jl} and λ_l are Lagrange multipliers and $\mathbf{P}_l = [p_{1l} \ \ \cdots \ \ p_{Ml}]$. The value of $S(\mathbf{P}_l)$ can be simplified as

$$
\begin{aligned}
S\left(\mathbf{P}_l\right) &= \sum_{i=1}^{N}\sum_{j=1}^{NMS-1}\left(v_{l,i}^{(j)}\right)^2 + 4\sum_{i=1}^{N}\sum_{j=1}^{NMS-1}\left(\sum_{h=1}^{M}\tilde{v}_{h,i}^{(j-1)}p_{hl}\right)^2 - 4\sum_{i=1}^{N}\sum_{j=1}^{NMS-1}v_{l,i}^{(j)}\sum_{h=1}^{M}\tilde{v}_{h,i}^{(j-1)}p_{hl} \\
&= \sum_{i=1}^{N}\sum_{j=1}^{NMS-1}\left(v_{l,i}^{(j)}\right)^2 + 4\sum_{i=1}^{N}\sum_{j=1}^{NMS-1}\sum_{h=1}^{M}\sum_{k=1}^{M}\tilde{v}_{h,i}^{(j-1)}\tilde{v}_{k,i}^{(j-1)}p_{hl}p_{kl} - 4\sum_{i=1}^{N}\sum_{j=1}^{NMS-1}v_{l,i}^{(j)}\sum_{h=1}^{M}\tilde{v}_{h,i}^{(j-1)}p_{hl} \\
&= \sum_{i=1}^{N}\sum_{j=1}^{NMS-1}\left(v_{l,i}^{(j)}\right)^2 + 4\sum_{j=1}^{NMS-1}\sum_{h=1}^{M}\left[\sum_{k=1}^{M}\sum_{i=1}^{N}\left(v_{h,i}^{(j-1)}v_{k,i}^{(j-1)}p_{hl}p_{kl} - \eta_{h,i}^{(j-1)}v_{k,i}^{(j-1)}p_{hl}p_{kl} - \eta_{k,i}^{(j-1)}v_{h,i}^{(j-1)}p_{hl}p_{kl} + \eta_{h,i}^{(j-1)}\eta_{k,i}^{(j-1)}p_{hl}p_{kl}\right)\right] \\
&\quad - 4\sum_{j=1}^{NMS-1}\sum_{i=1}^{N}v_{l,i}^{(j)}\sum_{h=1}^{M}v_{h,i}^{(j-1)}p_{hl} - \eta_{h,i}^{(j)}p_{hl}, \\
&= \sum_{i=1}^{N}\sum_{j=1}^{NMS-1}\left(v_{l,i}^{(j)}\right)^2 + 4\sum_{j=1}^{NMS-1}\sum_{h=1}^{M}\sum_{k=1}^{M}\sum_{i=1}^{N}v_{h,i}^{(j-1)}v_{k,i}^{(j-1)}p_{hl}p_{kl} - 4\sum_{j=1}^{NMS-1}\sum_{i=1}^{N}v_{l,i}^{(j)}\sum_{h=1}^{M}v_{h,i}^{(j-1)}p_{hl} \\
&\quad - 4\sum_{j=1}^{NMS-1}\sum_{h=1}^{M}\sum_{k=1}^{M}\sum_{i=1}^{N}\left(\eta_{h,i}^{(j-1)}v_{k,i}^{(j-1)}p_{hl}p_{kl} + \eta_{k,i}^{(j-1)}v_{h,i}^{(j-1)}p_{hl}p_{kl} - \eta_{h,i}^{(j-1)}\eta_{k,i}^{(j-1)}p_{hl}p_{kl}\right) + 2\sum_{j=1}^{NMS-1}\sum_{h=1}^{M}\sum_{i=1}^{N}v_{l,i}^{(j)}\eta_{h,i}^{(j)}p_{hl} \\
&= \sum_{i=1}^{N}\sum_{j=1}^{NMS-1}\left(v_{l,i}^{(j)}\right)^2 + 4\sum_{i=1}^{N}\sum_{j=1}^{NMS-1}\left(\sum_{h=1}^{M}v_{h,i}^{(j-1)}p_{hl}\right)^2 - 4\sum_{j=1}^{NMS-1}\sum_{i=1}^{N}v_{l,i}^{(j)}\sum_{h=1}^{M}v_{h,i}^{(j-1)}p_{hl} + 4\sum_{j=1}^{NMS-1}\sum_{h=1}^{M}\sum_{k=1}^{M}\sum_{i=1}^{N}\eta_{h,i}^{(j-1)}\eta_{k,i}^{(j-1)}p_{hl}p_{kl} \\
&\quad - 4\sum_{j=1}^{NMS-1}\sum_{h=1}^{M}\sum_{i=1}^{N}\left(\eta_{h,i}^{(j-1)}\sum_{k=1}^{M}v_{k,i}^{(j-1)}p_{hl}p_{kl}\right) - 4\sum_{j=1}^{NMS-1}\sum_{k=1}^{M}\sum_{i=1}^{N}\left(\eta_{k,i}^{(j-1)}\sum_{h=1}^{M}v_{h,i}^{(j-1)}p_{hl}p_{kl}\right) + 4\sum_{j=1}^{NMS-1}\sum_{h=1}^{M}\sum_{i=1}^{N}v_{l,i}^{(j)}\eta_{h,i}^{(j)}p_{hl}, \\
&= \sum_{i=1}^{N}\sum_{j=1}^{NMS-1}\left(v_{l,i}^{(j)} - 2\sum_{h=1}^{M}v_{h,i}^{(j-1)}p_{hl}\right)^2 + 4\sum_{j=1}^{NMS-1}\sum_{h=1}^{M}\sum_{k=1}^{M}p_{hl}p_{kl}\sum_{i=1}^{N}\eta_{h,i}^{(j-1)}\eta_{k,i}^{(j-1)} - 4\sum_{j=1}^{NMS-1}\sum_{h=1}^{M}\sum_{k=1}^{M}p_{hl}p_{kl}\sum_{i=1}^{N}\eta_{h,i}^{(j-1)}v_{k,i}^{(j-1)} \\
&\quad + 4\sum_{j=1}^{NMS-1}\sum_{h=1}^{M}p_{hl}\sum_{i=1}^{N}v_{l,i}^{(j)}\eta_{h,i}^{(j)},
\end{aligned}
\tag{S5}
$$

If either of the constraints in (S2-b) is inactive (is not satisfied with equality), the corresponding Lagrange multiplier is set to zero. And if either of them is active the value of p_{jl} is obtained directly from (S2-b). Hence, here we solve the problem when the set of constraints in (S2-b) is not active, and compute the derivative of (S5) with respect to p_{ql} and λ_l , $q,l \in \left[1,M\right]$. We have

$$
\begin{aligned}
\frac{\partial S_U\left(\mathbf{P}\right)}{\partial p_{ql}} = &-4\sum_{i=1}^{N}\sum_{j=1}^{NMS-1}v_{q,i}^{(j-1)}\left(v_{l,i}^{(j)} - 2\sum_{h=1}^{M}v_{h,i}^{(j-1)}p_{hl}\right) + 8\sum_{j=1}^{NMS-1}\sum_{h=1}^{M}p_{hl}\sum_{i=1}^{N}\eta_{q,i}^{(j-1)}\eta_{h,i}^{(j-1)} \\
&-8\sum_{j=1}^{NMS-1}\sum_{h=1}^{M}p_{hl}\sum_{i=1}^{N}\eta_{q,i}^{(j-1)}v_{h,i}^{(j-1)} + 4\sum_{j=1}^{NMS-1}\sum_{i=1}^{N}v_{q,i}^{(j)}\eta_{l,i}^{(j)} + \lambda_l,
\end{aligned}
\tag{S6-a}
$$

$$
\frac{\partial S_U\left(\mathbf{P}\right)}{\partial \lambda_l} = \left(\sum_{j=1}^{M}p_{jl} - 1\right), \tag{S6-b}
$$

By dividing both sides of (S6-a) by N and because the noise of different samples are centered processes, we have

$$
\begin{aligned}
\frac{1}{N}\frac{\partial S\left(\mathbf{P}_l\right)}{\partial p_{ql}} &= -\frac{4}{N}\left(\sum_{i=1}^{N}\sum_{j=1}^{NMS-1} v_{q,i}^{(j-1)}\left(v_{l,i}^{(j)} - 2\sum_{h=1}^{M} v_{h,i}^{(j-1)} p_{hl}\right) - 2\sum_{j=1}^{NMS-1}\sum_{h=1}^{M} p_{hl}\sum_{i=1}^{N}\eta_{q,i}^{(j-1)}\eta_{h,i}^{(j-1)} + \frac{\lambda_l}{4}\right) \\
&= -\frac{4}{N}\left(0.5\sum_{i=1}^{N}\sum_{j=1}^{NMS-1} v_{q,i}^{(j-1)} v_{l,i}^{(j)} - \sum_{h=1}^{M}\left(v_{q,i}^{(j-1)} v_{h,i}^{(j-1)} + \eta_{q,i}^{(j-1)}\eta_{h,i}^{(j-1)}\right) p_{hl} + \frac{\lambda_l}{4}\right)
\end{aligned}
\tag{S7}
$$

By writing (S7) in matrix form, we have

$$
\begin{bmatrix} \sum_{i=1}^{N}\sum_{j=1}^{NMS-1}\left(v_{q,i}^{(j-1)} v_{1,i}^{(j-1)} + \eta_{q,i}^{(j-1)}\eta_{1,i}^{(j-1)}\right) & \cdots & \sum_{i=1}^{N}\sum_{j=1}^{NMS-1}\left(v_{q,i}^{(j-1)} v_{M,i}^{(j-1)} + \eta_{q,i}^{(j-1)}\eta_{M,i}^{(j-1)}\right) \end{bmatrix} \begin{bmatrix} p_{1l} \\ \vdots \\ p_{Ml} \end{bmatrix} = 0.5\sum_{i=1}^{N}\sum_{j=1}^{NMS-1} v_{q,i}^{(j-1)} v_{l,i}^{(j)} - \frac{\lambda_l}{4}
\tag{S8}
$$

If we write the above equation for all values of q, we have following equations

$$
\begin{bmatrix} \sum_{j=1}^{NMS-1}\sum_{i=1}^{N}\left(v_{1,i}^{(j-1)} v_{1,i}^{(j-1)} + \eta_{1,i}^{(j-1)}\eta_{1,i}^{(j-1)}\right) & \cdots & \sum_{j=1}^{NMS-1}\sum_{i=1}^{N}\left(v_{1,i}^{(j-1)} v_{M,i}^{(j-1)} + \eta_{1,i}^{(j-1)}\eta_{M,i}^{(j-1)}\right) \\ \vdots & \ddots & \vdots \\ \sum_{j=1}^{NMS-1}\sum_{i=1}^{N}\left(v_{M,i}^{(j-1)} v_{1,i}^{(j-1)} + \eta_{M,i}^{(j-1)}\eta_{1,i}^{(j-1)}\right) & \cdots & \sum_{j=1}^{NMS-1}\sum_{i=1}^{N}\left(v_{M,i}^{(j-1)} v_{M,i}^{(j-1)} + \eta_{M,i}^{(j-1)}\eta_{M,i}^{(j-1)}\right) \end{bmatrix} \begin{bmatrix} p_{1l} \\ \vdots \\ p_{Ml} \end{bmatrix} = 0.5\begin{bmatrix} \sum_{i=1}^{N}\sum_{j=1}^{NMS-1} v_{1,i}^{(j-1)} v_{l,i}^{(j)} \\ \vdots \\ \sum_{i=1}^{N}\sum_{j=1}^{NMS-1} v_{M,i}^{(j-1)} v_{l,i}^{(j)} \end{bmatrix} - \frac{\lambda_l}{4}
\tag{S9}
$$

Hence, $\mathbf{P}_l$ is given by

$$
\begin{bmatrix} p_{1l} \\ \vdots \\ p_{Ml} \end{bmatrix} = 0.5\left(\begin{bmatrix} \sum_{j=1}^{NMS-1}\sum_{i=1}^{N} v_{1,i}^{(j-1)} v_{1,i}^{(j-1)} & \cdots & \sum_{j=1}^{NMS-1}\sum_{i=1}^{N} v_{1,i}^{(j-1)} v_{M,i}^{(j-1)} \\ \vdots & \ddots & \vdots \\ \sum_{j=1}^{NMS-1}\sum_{i=1}^{N} v_{M,i}^{(j-1)} v_{1,i}^{(j-1)} & \cdots & \sum_{j=1}^{NMS-1}\sum_{i=1}^{N} v_{M,i}^{(j-1)} v_{M,i}^{(j-1)} \end{bmatrix} + \begin{bmatrix} \sum_{j=1}^{NMS-1}\sum_{i=1}^{N} \eta_{1,i}^{(j-1)}\eta_{1,i}^{(j-1)} & \cdots & \sum_{j=1}^{NMS-1}\sum_{i=1}^{N} \eta_{1,i}^{(j-1)}\eta_{M,i}^{(j-1)} \\ \vdots & \ddots & \vdots \\ \sum_{j=1}^{NMS-1}\sum_{i=1}^{N} \eta_{M,i}^{(j-1)}\eta_{1,i}^{(j-1)} & \cdots & \sum_{j=1}^{NMS-1}\sum_{i=1}^{N} \eta_{M,i}^{(j-1)}\eta_{M,i}^{(j-1)} \end{bmatrix}\right)^{-1}
$$

$$
\begin{bmatrix} \sum_{i=1}^{N}\sum_{j=1}^{MMS-1} v_{1,i}^{(j-1)} v_{l,i}^{(j)} - \frac{\lambda_l}{4} \\ \vdots \\ \sum_{i=1}^{N}\sum_{j=1}^{NMS-1} v_{M,i}^{(j-1)} v_{l,i}^{(j)} - \frac{\lambda_l}{4} \end{bmatrix}
\tag{S10}
$$

If the variance of noise for each type of cell in all samples is considered equal, i.e., $\sigma_{ji}^2 = \sigma_j^2$, we have

$$\begin{bmatrix} p_{1l} \\ \vdots \\ p_{Ml} \end{bmatrix} = 0.5\left(\begin{bmatrix} \sum_{j=1}^{NMS-1}\sum_{i=1}^{N} v_{1,i}^{(j-1)} v_{1,i}^{(j-1)} & \cdots & \sum_{j=1}^{NMS-1}\sum_{i=1}^{N} v_{1,i}^{(j-1)} v_{M,i}^{(j-1)} \\ \vdots & \ddots & \vdots \\ \sum_{j=1}^{NMS-1}\sum_{i=1}^{N} v_{M,i}^{(j-1)} v_{1,i}^{(j-1)} & \cdots & \sum_{j=1}^{NMS-1}\sum_{i=1}^{N} v_{M,i}^{(j-1)} v_{M,i}^{(j-1)} \end{bmatrix} + N\left(NMS-1\right)\begin{bmatrix} \sigma_1^2 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & \sigma_M^2 \end{bmatrix}\right)^{-1}$$

$$\begin{bmatrix} \sum_{i=1}^{N}\sum_{j=1}^{NMS-1} v_{1,i}^{(j-1)} v_{l,i}^{(j)} - \frac{\lambda_l}{4} \\ \vdots \\ \sum_{i=1}^{N}\sum_{j=1}^{NMS-1} v_{M,i}^{(j-1)} v_{l,i}^{(j)} - \frac{\lambda_l}{4} \end{bmatrix} \tag{S11}$$

which can be simplified to

$$\hat{\mathbf{P}}_l = 0.5\left(\left(\mathbf{V}_{:,1:N}^{(0:NMS-2)}\right)^{\dagger}\left(\mathbf{V}_{:,1:N}^{(0:NMS-2)}\right) + N\left(NMS-1\right)\mathbf{R}_n\right)^{-1}\left(\mathbf{V}_{:,1:N}^{(0:NMS-1)}\right)^{\dagger}\mathbf{V}_{l,(1:N)}^{(1:NMS-1)} - \Lambda_l, \tag{S12}$$

where,

$$\mathbf{V}_{:,1:N}^{(0:NMS-2)} = \begin{bmatrix} v_{1,1}^{(0)} & \cdots & v_{M,1}^{(0)} \\ \vdots & \ddots & \vdots \\ v_{1,1}^{(NMS-2)} & \cdots & v_{M,1}^{(NMS-2)} \\ \vdots & \vdots & \vdots \\ v_{1,N}^{(0)} & \cdots & v_{M,N}^{(0)} \\ \vdots & \ddots & \vdots \\ v_{1,N}^{(NMS-2)} & \cdots & v_{M,N}^{(NMS-2)} \end{bmatrix}, \tag{S13}$$

and

$$\mathbf{V}_{l,(1:N)}^{(1:NMS-1)} = \begin{bmatrix} v_{l,1}^{(1)} & \ldots & v_{l,1}^{(M)} & \ldots & v_{l,N}^{(1)} & \ldots & v_{l,N}^{(NMS-1)} \end{bmatrix}^{\dagger} \tag{S14}$$

and

$$\mathbf{R}_n = \begin{bmatrix} \sigma_1^2 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & \sigma_M^2 \end{bmatrix} \tag{S15}$$

and

$$\Lambda_l = \begin{bmatrix} \frac{\lambda_l}{4} & \cdots & \frac{\lambda_l}{4} \end{bmatrix}^{\dagger} \tag{S16}$$

where λ_l is obtained from the following equation for each value of l

$$\sum_{h=1}^{M} p_{hl} = 1 \tag{S17}$$

As stated, in the above derivations we did not explicitly incorporated the constraints in (S2-b) and assumed they are inactive. If the assumption is not valid, we will arrive at values of p_{hl} possibly greater than one or negative. In this case, we enforce the violated constraint with equality and solve the optimization problem again. In case, there are multiple such violated constraints, this process is repeated for different combinations of enforced constraints (see [3] pp.314-357 for details).

Section C

In this Section, we derive the ML estimator for the transition probability of the cell proliferation Markov chain with observations made in the presence of additive white Gaussian noise. In the first step, using a joint probability formula for $\hat{\mathbf{P}}_{ML}$, we have

$$\begin{aligned}
\hat{\mathbf{P}}_{ML} &= \max_{\mathbf{P}} P\left(v_{1,1}^{(0)},\ldots,v_{1,N}^{(0)},\ldots,v_{M,1}^{(0)},\ldots,v_{M,N}^{(0)},\ldots,v_{1,1}^{(NMS-1)},\ldots,v_{1,N}^{(NMS-1)},\ldots,v_{M,N}^{(NMS-1)},\ldots,v_{M,N}^{(NMS-1)}\middle|\mathbf{P}\right)\\
&\overset{(a)}{=} \max_{\mathbf{P}} P\left(v_{1,1}^{(0)},\ldots,v_{1,N}^{(0)},\ldots,v_{M,1}^{(0)},\ldots,v_{M,N}^{(0)}\middle|\mathbf{P}\right)\\
&\qquad P\left(v_{1,1}^{(1)},\ldots,v_{1,N}^{(1)},\ldots,v_{M,1}^{(1)},\ldots,v_{M,N}^{(1)}\middle|\mathbf{P},v_{1,1}^{(0)},\ldots,v_{1,N}^{(0)},\ldots,v_{M,1}^{(0)},\ldots,v_{M,N}^{(0)}\right)\ldots\\
&\qquad P\left(v_{1,1}^{(NMS-1)},\ldots,v_{1,N}^{(NMS-1)},\ldots,v_{M,1}^{(NMS-1)},\ldots,v_{M,N}^{(NMS-1)}\middle|\mathbf{P},v_{1,1}^{(0)},\ldots,v_{1,N}^{(0)},\ldots,v_{M,1}^{(0)},\ldots,v_{M,N}^{(0)},\ldots,\right.\\
&\qquad\quad \left.v_{1,1}^{(NMS-2)},\ldots,v_{1,N}^{(NMS-2)},\ldots,v_{M,1}^{(NMS-2)},\ldots,v_{M,N}^{(NMS-2)}\right)\\
&\overset{(b)}{=} \max_{\mathbf{P}} P\left(v_{1,1}^{(0)},\ldots,v_{1,N}^{(0)},\ldots,v_{M,1}^{(0)},\ldots,v_{M,N}^{(0)}\middle|\mathbf{P}\right)\\
&\qquad P\left(v_{1,1}^{(1)},\ldots,v_{1,N}^{(1)},\ldots,v_{M,1}^{(1)},\ldots,v_{M,N}^{(1)}\middle|\mathbf{P},v_{1,1}^{(0)},\ldots,v_{1,N}^{(0)},\ldots,v_{M,1}^{(0)},\ldots,v_{M,N}^{(0)}\right)\ldots\\
&\qquad P\left(v_{1,1}^{(NMS-1)},\ldots,v_{1,N}^{(NMS-1)},\ldots,v_{M,1}^{(NMS-1)},\ldots,v_{M,N}^{(NMS-1)}\middle|\mathbf{P},v_{1,1}^{(NMS-2)},\ldots,v_{1,N}^{(NMS-2)},\ldots,v_{M,1}^{(NMS-2)},\ldots,v_{M,N}^{(NMS-2)}\right),
\end{aligned} \tag{S18}$$

(a) is obtained using the chain rule and (b) is due to first order Markov property of population size. Moreover, it is assumed that the observations are independent, hence, in (S18) we have

$$P\left(v_{1,1}^{(0)},\ldots,v_{1,N}^{(0)},\ldots,v_{M,1}^{(0)},\ldots,v_{M,N}^{(0)}\,\middle|\,\mathbf{P}\right)=\prod_{i=1}^{N}\prod_{j=1}^{M}P\left(v_{j,i}^{(0)}\,\middle|\,\mathbf{P}\right)$$

$$=\prod_{i=1}^{N}\prod_{j=1}^{M}\frac{1}{\sqrt{2\pi}\sigma_{ji}}\exp\left(\frac{-\left(v_{j,i}^{(0)}-\tilde{v}_{j,i}^{(0)}\right)^{2}}{2\sigma_{ji}^{2}}\right) \tag{S19}$$

$$=\frac{1}{\left(2\pi\right)^{MN/2}\prod_{i=1}^{N}\prod_{j=1}^{M}\sigma_{ji}}\exp\left(-\sum_{i=1}^{N}\sum_{j=1}^{M}\frac{\left(v_{j,i}^{(0)}-\tilde{v}_{j,i}^{(0)}\right)^{2}}{2\sigma_{ji}^{2}}\right),$$

$$P\left(v_{1,1}^{(1)},\ldots,v_{1,N}^{(1)},\ldots,v_{M,1}^{(1)},\ldots,v_{M,N}^{(1)}\,\middle|\,\mathbf{P},v_{1,1}^{(0)},\ldots,v_{1,N}^{(0)},\ldots,v_{M,1}^{(0)},\ldots,v_{M,N}^{(0)}\right)=\prod_{i=1}^{N}\prod_{j=1}^{M}P\left(v_{j,i}^{(1)}\,\middle|\,\mathbf{P},v_{1,1}^{(0)},\ldots,v_{1,N}^{(0)},\ldots,v_{M,1}^{(0)},\ldots,v_{M,N}^{(0)}\right)$$

$$=\prod_{i=1}^{N}\prod_{j=1}^{M}\frac{1}{\sqrt{2\pi}\sigma_{ji}}\exp\left(-\frac{\left(v_{j,i}^{(1)}-2\sum_{h=1}^{M}\tilde{v}_{h,i}^{(0)}p_{hj}\right)^{2}}{2\sigma_{ji}^{2}}\right)$$

$$=\frac{1}{\left(2\pi\right)^{MN/2}\prod_{i=1}^{N}\prod_{j=1}^{M}\sigma_{ji}}\exp\left(-\sum_{i=1}^{N}\sum_{j=1}^{M}\frac{\left(v_{j,i}^{(1)}-2\sum_{h=1}^{M}\tilde{v}_{h,i}^{(0)}p_{hj}\right)^{2}}{2\sigma_{ji}^{2}}\right) \tag{S20}$$

$$=\frac{1}{\left(2\pi\right)^{MN/2}\prod_{i=1}^{N}\prod_{j=1}^{M}\sigma_{ji}}\exp\left(-\sum_{i=1}^{N}\sum_{j=1}^{M}\frac{\left(v_{j,i}^{(1)}-2\sum_{h=1}^{M}\tilde{v}_{h,i}^{(0)}p_{hj}\right)^{2}}{2\sigma_{ji}^{2}}\right)$$

$$P\left(v_{1,1}^{(NMS-1)},\ldots,v_{1,N}^{(NMS-1)},\ldots,v_{M,1}^{(1)},\ldots,v_{M,N}^{(1)}\,\middle|\,\mathbf{P},v_{1,1}^{(NMS-2)},\ldots,v_{1,N}^{(NMS-2)},\ldots,v_{M,1}^{(NMS-2)},\ldots,v_{M,N}^{(NMS-2)}\right)=$$

$$\prod_{i=1}^{N}\prod_{j=1}^{M}P\left(v_{j,i}^{(NMS-1)}\,\middle|\,\mathbf{P},v_{1,1}^{(NMS-2)},\ldots,v_{1,N}^{(NMS-2)},\ldots,v_{M,1}^{(NMS-2)},\ldots,v_{M,N}^{(NMS-2)}\right)=$$

$$\prod_{i=1}^{N}\prod_{j=1}^{M}\frac{1}{\sqrt{2\pi}\sigma_{ji}}\exp\left(\frac{-\left(v_{j,i}^{(NMS-1)}-2\sum_{h=1}^{M}\tilde{v}_{h,i}^{(NMS-2)}p_{hj}\right)^{2}}{2\sigma_{ji}^{2}}\right)=$$

$$\frac{1}{\left(2\pi\right)^{MN/2}\prod_{i=1}^{N}\prod_{j=1}^{M}\sigma_{ji}}\exp\left(-\sum_{i=1}^{N}\sum_{j=1}^{M}\frac{\left(v_{j,i}^{(NMS-1)}-2\sum_{h=1}^{M}\tilde{v}_{h,i}^{(NMS-2)}p_{hj}\right)^{2}}{2\sigma_{ji}^{2}}\right). \tag{S21}$$

where, σ_{ji}^{2}, $j \in [1, M]$ denotes the standard deviation of Gaussian noise for cell type j in sample i. Replacing (S19)-(S21) in (S18), we have

$$P\left(v_{1,1}^{(0)},\ldots,v_{1,N}^{(0)},\ldots,v_{M,1}^{(0)},\ldots,v_{M,N}^{(0)},\ldots,v_{1,1}^{(NMS-1)},\ldots,v_{1,N}^{(NMS-1)},\ldots,v_{M,N}^{(NMS-1)},\ldots,v_{M,N}^{(NMS-1)} \middle| \mathbf{P}\right) = \frac{1}{(2\pi)^{(MN)NMS/2}\left(\prod_{i=1}^{N}\prod_{j=1}^{M}\sigma_{ji}\right)^{NMS}} \exp\left(-\sum_{i=1}^{N}\sum_{j=1}^{M}\frac{\left(v_{j,i}^{(0)}-\tilde{v}_{j,i}^{(0)}\right)^2}{2\sigma_{ji}^2}-\sum_{i=1}^{N}\sum_{j=1}^{M}\frac{\left(v_{j,i}^{(1)}-2\sum_{h=1}^{M}\tilde{v}_{h,i}^{(0)}p_{hj}\right)^2}{2\sigma_{ji}^2}-\ldots-\sum_{i=1}^{N}\sum_{j=1}^{M}\frac{\left(v_{j,i}^{(NMS-1)}-2\sum_{h=1}^{M}\tilde{v}_{h,i}^{(NMS-2)}p_{hj}\right)^2}{2\sigma_{ji}^2}\right) \tag{S22}$$

Taking the Logarithm of the above equation and ignoring the constant terms, we have

$$\log P\left(v_{1,1}^{(0)},\ldots,v_{1,N}^{(0)},\ldots,v_{M,1}^{(0)},\ldots,v_{M,N}^{(0)},\ldots,v_{1,1}^{(NMS-1)},\ldots,v_{1,N}^{(NMS-1)},\ldots,v_{M,N}^{(NMS-1)},\ldots,v_{M,N}^{(NMS-1)} \middle| \mathbf{P}\right) = -NMS\log\left(\left(\sqrt{2\pi}\right)^{MN}\prod_{i=1}^{N}\prod_{j=1}^{M}\sigma_{ji}\right)-\sum_{i=1}^{N}\sum_{j=1}^{M}\frac{\left(v_{j,i}^{(0)}-\tilde{v}_{j,i}^{(0)}\right)^2}{2\sigma_{ji}^2}-\sum_{i=1}^{N}\sum_{j=1}^{M}\frac{\left(v_{j,i}^{(1)}-2\sum_{i=1}^{M}\tilde{v}_{h,i}^{(0)}p_{hj}\right)^2}{2\sigma_{ji}^2}-\ldots -\sum_{i=1}^{N}\sum_{j=1}^{M}\frac{\left(v_{j,i}^{(NMS-1)}-2\sum_{i=1}^{M}\tilde{v}_{h,i}^{(NMS-2)}p_{hj}\right)^2}{2\sigma_{ji}^2}. \tag{S23}$$

Taking the derivative with respect to p_{kl} and setting it to zero, we have M equations as follows

$$\sum_{i=1}^{N}\left(\frac{\tilde{v}_{k,i}^{(0)}\left(v_{l,i}^{(1)}-2\sum_{h=1}^{M}\tilde{v}_{h,i}^{(0)}p_{hl}\right)}{2\sigma_{li}^2}+\ldots+\frac{\tilde{v}_{k,i}^{(NMS-2)}\left(v_{l,i}^{(NMS-1)}-2\sum_{i=1}^{M}\tilde{v}_{h,i}^{(NMS-2)}p_{hl}\right)}{2\sigma_{li}^2}\right)=0,\Rightarrow$$

$$2\sum_{i=1}^{N}\sum_{j=1}^{NMS-1}\sum_{h=1}^{M}\frac{\tilde{v}_{k,i}^{(j-1)}\tilde{v}_{h,i}^{(j-1)}p_{hl}}{2\sigma_{li}^2}=\sum_{i=1}^{N}\sum_{j=1}^{NMS-1}\frac{\tilde{v}_{k,i}^{(j-1)}v_{l}^{(j)}}{2\sigma_{li}^2},\Rightarrow$$

$$\sum_{i=1}^{N}\begin{bmatrix}\tilde{v}_{k,i}^{(0)} & \tilde{v}_{k,i}^{(1)} & \cdots & \tilde{v}_{k,i}^{(NMS-2)}\end{bmatrix}\begin{bmatrix}2\sigma_{li}^{-2}\sum_{h=1}^{M}\tilde{v}_{h,i}^{(0)}p_{hl}\\ 2\sigma_{li}^{-2}\sum_{h=1}^{M}\tilde{v}_{h,i}^{(1)}p_{hl}\\ \vdots\\ 2\sigma_{li}^{-2}\sum_{h=1}^{M}\tilde{v}_{h,i}^{(NMS-2)}p_{hl}\end{bmatrix}=\sum_{i=1}^{N}\begin{bmatrix}\tilde{v}_{k,i}^{(0)} & \tilde{v}_{k,i}^{(1)} & \cdots & \tilde{v}_{k,i}^{(NMS-2)}\end{bmatrix}\begin{bmatrix}\sigma_{li}^{-2}v_{l,i}^{(1)}\\ \sigma_{li}^{-2}v_{l,i}^{(2)}\\ \vdots\\ \sigma_{li}^{-2}v_{l,i}^{(NMS-1)}\end{bmatrix}. \tag{S24}$$

In the setting under consideration, we make separate observations based on each sample, and attempt to obtain a common optimized transition probability for the underlying Markov process. As a result, we satisfy the above equation by enforcing the constraint for each sample. We have

$$\begin{bmatrix} \tilde{v}_{k,i}^{(0)} & \tilde{v}_{k,i}^{(1)} & \cdots & \tilde{v}_{k,i}^{(NMS-2)} \end{bmatrix} \begin{bmatrix} 2\sigma_{li}^{-2} \sum_{h=1}^{M} \tilde{v}_{h,i}^{(0)} p_{hl} \\ 2\sigma_{li}^{-2} \sum_{h=1}^{M} \tilde{v}_{h,i}^{(1)} p_{hl} \\ \vdots \\ 2\sigma_{li}^{-2} \sum_{h=1}^{M} \tilde{v}_{h,i}^{(NMS-2)} p_{hl} \end{bmatrix} = \begin{bmatrix} \tilde{v}_{k,i}^{(0)} & \tilde{v}_{k,i}^{(1)} & \cdots & \tilde{v}_{k,i}^{(NMS-2)} \end{bmatrix} \begin{bmatrix} \sigma_{li}^{-2} v_{l,i}^{(1)} \\ \sigma_{li}^{-2} v_{l,i}^{(2)} \\ \vdots \\ \sigma_{li}^{-2} v_{l,i}^{(NMS-1)} \end{bmatrix}. \tag{S25}$$

Hence for all values of k, we have following equations,

$$\begin{bmatrix} \tilde{v}_{1,i}^{(0)} & \tilde{v}_{1,i}^{(1)} & \cdots & \tilde{v}_{1,i}^{(NMS-2)} \\ \tilde{v}_{2,i}^{(0)} & \tilde{v}_{2,i}^{(1)} & \cdots & \tilde{v}_{2,i}^{(NMS-2)} \\ \vdots & \vdots & \ddots & \vdots \\ \tilde{v}_{M,i}^{(0)} & \tilde{v}_{M,i}^{(1)} & \cdots & \tilde{v}_{M,i}^{(NMS-2)} \end{bmatrix} \begin{bmatrix} 2\sigma_{li}^{-2} \sum_{h=1}^{M} \tilde{v}_{h,i}^{(0)} p_{il} \\ 2\sigma_{li}^{-2} \sum_{h=1}^{M} \tilde{v}_{h,i}^{(1)} p_{il} \\ \vdots \\ 2\sigma_{li}^{-2} \sum_{h=1}^{M} \tilde{v}_{h,i}^{(NMS-2)} p_{il} \end{bmatrix} = \begin{bmatrix} \tilde{v}_{1,i}^{(0)} & \tilde{v}_{1,i}^{(1)} & \cdots & \tilde{v}_{1,i}^{(NMS-2)} \\ \tilde{v}_{2,i}^{(0)} & \tilde{v}_{2,i}^{(1)} & \cdots & \tilde{v}_{2,i}^{(NMS-2)} \\ \vdots & \vdots & \ddots & \vdots \\ \tilde{v}_{M,i}^{(0)} & \tilde{v}_{M,i}^{(1)} & \cdots & \tilde{v}_{M,i}^{(NMS-2)} \end{bmatrix} \begin{bmatrix} \sigma_{li}^{-2} v_{l,i}^{(1)} \\ \sigma_{li}^{-2} v_{l,i}^{(2)} \\ \vdots \\ \sigma_{li}^{-2} v_{l,i}^{(NMS-1)} \end{bmatrix}, \tag{S26}$$

If matrix $\mathbf{V}_i$ is full column rank, we simply have

$$\begin{bmatrix} 2\sum_{h=1}^{M} \tilde{v}_{h,i}^{(0)} p_{il} \\ 2\sum_{h=1}^{M} \tilde{v}_{h,i}^{(1)} p_{il} \\ \vdots \\ 2\sum_{h=1}^{M} \tilde{v}_{h,i}^{(NMS-2)} p_{il} \end{bmatrix} = \begin{bmatrix} v_{l,i}^{(1)} \\ v_{l,i}^{(2)} \\ \vdots \\ v_{l,i}^{(NMS-1)} \end{bmatrix} \Rightarrow$$

$$2\begin{bmatrix} \tilde{v}_{1,i}^{(0)} & \tilde{v}_{2,i}^{(0)} & \cdots & \tilde{v}_{M,i}^{(0)} \\ v_{1,i}^{(1)} & v_{2,i}^{(1)} & \cdots & \tilde{v}_{M,i}^{(1)} \\ \vdots & \vdots & \ddots & \vdots \\ v_{1,i}^{(NMS-2)} & v_{2,i}^{(NMS-2)} & \cdots & \tilde{v}_{M,i}^{(NMS-2)} \end{bmatrix} \begin{bmatrix} p_{1l} \\ p_{2l} \\ \vdots \\ p_{Ml} \end{bmatrix} = \begin{bmatrix} v_{l,i}^{(1)} \\ v_{l,i}^{(2)} \\ \vdots \\ v_{l,i}^{(NMS-1)} \end{bmatrix}. \tag{S27}$$

For each value of $i \in [1, N]$, if $NMS - 1 < M$, the above system of linear equations for p_{1l} has infinitely many solutions, and is an underdetermined system. If $NMS - 1 = M$, the above system of linear equations has a single unique solution. Due to independency of noise in different samples, joint probability of observations in (18), can be factorized to multiplication of joint probability for N samples. Hence, the solution of (S27) maximizes each component of joint probability in (S18). If $NMS-1>M$, such a system has no solution, and is an over determined system. In this case, if we solve (S27) with ℓ_2 norm, we obtain the same results of Theorem 1.

Section D

In a Poisson process, the number of observed occurrences fluctuates about its mean $\tilde{v}_{j,i}^{(k)}$ with a standard deviation of $\sigma_{j,i}=\tilde{v}_{j,i}^{(k)}$. These fluctuations are due to what is known as *shot noise* and are signal dependent. In this Section, the system of equations for cell proliferation when observations are corrupted by shot noise is derived using an ML estimator. In shot noise, the observations are Poisson distributed, and the terms in (S18) may be computed as follows

$$\begin{aligned}P\left(v_{1,1}^{(0)},\dots,v_{1,N}^{(0)},\dots,v_{M,1}^{(0)},\dots,v_{M,N}^{(0)}\middle|\mathbf{P}\right)&=\prod_{i=1}^{N}\prod_{j=1}^{M}P\left(v_{j,i}^{(0)}\middle|\mathbf{P}\right)\\&=\prod_{i=1}^{N}\prod_{j=1}^{M}\frac{\left(\tilde{v}_{j,i}^{(0)}\right)^{v_j^{(0)}}}{v_{j,i}^{(0)}!}\exp(-\tilde{v}_{j,i}^{(0)})\end{aligned}\tag{S28}$$

$$\begin{aligned}&P\left(v_{1,1}^{(1)},\dots,v_{1,N}^{(1)},\dots,v_{M,1}^{(1)},\dots,v_{M,N}^{(1)}\middle|\mathbf{P},v_{1,1}^{(0)},\dots,v_{1,N}^{(0)},\dots,v_{M,1}^{(0)},\dots,v_{M,N}^{(0)}\right)\\&=\prod_{i=1}^{N}\prod_{j=1}^{M}P\left(v_{j,i}^{(1)}\middle|\mathbf{P},v_{1,1}^{(0)},\dots,v_{1,N}^{(0)},\dots,v_{M,1}^{(0)},\dots,v_{M,N}^{(0)}\right)\\&=\prod_{i=1}^{N}\prod_{j=1}^{M}\frac{\left(2\sum_{h=1}^{M}\tilde{v}_{h,i}^{(0)}p_{hj}\right)^{v_{j,i}^{(1)}}}{v_{j,i}^{(1)}!}\exp(-2\sum_{h=1}^{M}\tilde{v}_{h,i}^{(0)}p_{hj})\end{aligned}\tag{S29}$$

$$\begin{aligned}&P\left(v_{1,1}^{(NMS-1)},\dots,v_{1,N}^{(NMS-1)},\dots,v_{M,1}^{(NMS-1)},\dots,v_{M,N}^{(NMS-1)}\middle|\mathbf{P},v_{1,1}^{(NMS-2)},\dots,v_{1,N}^{(NMS-2)},\dots,v_{M,1}^{(NMS-2)},\dots,v_{M,N}^{(NMS-2)}\right)\\&=\prod_{i=1}^{N}\prod_{j=1}^{M}P\left(v_{j,i}^{(NMS-1)}\middle|\mathbf{P},v_{1,1}^{(NMS-2)},\dots,v_{1,N}^{(NMS-2)},\dots,v_{M,1}^{(NMS-2)},\dots,v_{M,N}^{(NMS-2)}\right)\\&=\prod_{i=1}^{N}\prod_{j=1}^{M}\frac{\left(2\sum_{h=1}^{M}\tilde{v}_{h,i}^{(NMS-2)}p_{ij}\right)^{v_{ji}^{(NMS-1)}}}{v_{j,i}^{(NMS-1)}!}\exp(-2\sum_{h=1}^{M}\tilde{v}_{h,i}^{(NMS-2)}p_{hj})\end{aligned}\tag{S30}$$

in which $\tilde{v}_{j,i}^{(0)}$ is the true initial population size of cell type j in sample i. Hence, using (S28) – (S30) in (S18), we have

$$P\left(v_{1,1}^{(0)},...,v_{1,N}^{(0)},...,v_{M,N}^{(0)},...,v_{M,N}^{(NMS-1)},...,v_{M,N}^{(NMS-1)}\middle|\mathbf{P}\right)=\prod_{i=1}^{N}\prod_{j=1}^{M}\frac{\left(\tilde{v}_{j,i}^{(0)}\right)^{v_{j,i}^{(0)}}}{v_{j,i}^{(0)}!}\prod_{i=1}^{N}\prod_{j=1}^{M}\frac{\left(2\sum_{h=1}^{M}\tilde{v}_{h,i}^{(0)}p_{hj}\right)^{v_{j,i}^{(1)}}}{v_{j,i}^{(1)}!}\cdots$$

$$\prod_{i=1}^{N}\prod_{j=1}^{M}\frac{\left(2\sum_{h=1}^{M}\tilde{v}_{h,i}^{(NMS-2)}p_{ij}\right)^{v_{ji}^{(M)}}}{v_{j,i}^{(NMS-1)}!} \tag{S31}$$

$$\prod_{i=1}^{N}\prod_{j=1}^{M}\exp\left(-\left(\tilde{v}_{j,i}^{(0)}+2\sum_{i=1}^{M}\tilde{v}_{h,i}^{(0)}p_{hj}+...+2\sum_{i=1}^{M}\tilde{v}_{h,i}^{(NMS-2)}p_{hj}\right)\right)$$

Taking the Logarithm of the above equation and ignoring the constant terms, we have

$$\log P\left(v_{1,1}^{(0)},...,v_{1,N}^{(0)},...,v_{M,N}^{(0)},...,v_{M,N}^{(NMS-1)},...,v_{M,N}^{(NMS-1)}\middle|\mathbf{P}\right)=$$

$$\sum_{i=1}^{N}\sum_{j=1}^{M}\left(v_{j,i}^{(0)}\log_e\tilde{v}_{j,i}^{(0)}-\log_e v_{j,i}^{(0)}!+v_{j,i}^{(1)}\log_e 2\sum_{h=1}^{M}\tilde{v}_{h,i}^{(0)}p_{hj}-\log_e v_{j,i}^{(1)}!...+v_{j,i}^{(NMS-1)}\log_e 2\sum_{h=1}^{M}\tilde{v}_{h,i}^{(NMS-2)}p_{hj}-\log_e v_{j,i}^{(NMS-1)}!\right. \tag{S32}$$

$$\left.-\tilde{v}_{j,i}^{(0)}-2\sum_{i=1}^{M}\tilde{v}_{h,i}^{(0)}p_{hj}-...-2\sum_{i=1}^{M}\tilde{v}_{h,i}^{(NMS-2)}p_{hj}\right)$$

Computing the derivative with respect to p_{kl} and setting the result to zero, we have *M* equations

$$\sum_{i=1}^{N}\frac{v_{l,i}^{(1)}\tilde{v}_{k,i}^{(0)}}{\sum_{h=1}^{M}\tilde{v}_{h,i}^{(0)}p_{hl}}+...+\frac{v_{l,i}^{(NMS-1)}\tilde{v}_{k,i}^{(NMS-2)}}{\sum_{h=1}^{M}\tilde{v}_{h,i}^{(NMS-2)}p_{hl}}-2\left(\tilde{v}_{k,i}^{(0)}+...+\tilde{v}_{k,i}^{(NMS-2)}\right)=0\Rightarrow$$

$$\sum_{i=1}^{N}\frac{v_{l,i}^{(1)}\tilde{v}_{k,i}^{(0)}}{\sum_{h=1}^{M}\tilde{v}_{h,i}^{(0)}p_{hl}}+...+\frac{v_{l,i}^{(NMS-1)}\tilde{v}_{k,i}^{(NMS-2)}}{\sum_{h=1}^{M}\tilde{v}_{h,i}^{(NMS-2)}p_{hl}}=\sum_{i=1}^{N}2\left(\tilde{v}_{k,i}^{(0)}+...+\tilde{v}_{k,i}^{(NMS-2)}\right)\Rightarrow$$

$$\sum_{i=1}^{N}\left(v_{l,i}^{(1)}\tilde{v}_{k,i}^{(0)}\prod_{\substack{q=1\\(q,j)\neq(i,0)}}^{N}\prod_{j=0,}^{NMS-2}\sum_{h=1}^{M}\tilde{v}_{h,i}^{(j)}p_{hl}+...+v_{l,i}^{(NMS-1)}\tilde{v}_{k,i}^{(NMS-2)}\prod_{\substack{q=1\\(q,j)\neq(i,M-1)}}^{N}\prod_{j=0}^{NMS-2}\sum_{h=1}^{M}\tilde{v}_{h,q}^{(j)}p_{hl}\right)=$$

$$\sum_{i=1}^{N}2\left(\tilde{v}_{k,i}^{(0)}+...+\tilde{v}_{k,i}^{(NMS-2)}\right)\prod_{q=1}^{N}\prod_{j=0}^{NMS-2}\sum_{h=1}^{M}\tilde{v}_{h,q}^{(j)}p_{hl}\Rightarrow$$

$$\sum_{i=1}^{N}\sum_{r=1}^{NMS-1}v_{l,i}^{(r)}\tilde{v}_{k,i}^{(r-1)}\prod_{\substack{q=1\\(q,j)\neq(i,r-1)}}^{N}\prod_{j=0}^{NMS-2}\sum_{h=1}^{M}\tilde{v}_{h,q}^{(j)}p_{hl}=2\sum_{i=1}^{N}\sum_{r=1}^{NMS-1}\tilde{v}_{k,i}^{(r-1)}\prod_{q=1}^{N}\prod_{j=0}^{NMS-2}\sum_{h=1}^{M}\tilde{v}_{h,q}^{(j)}p_{hl} \tag{S33}$$

Eq. (S33) in matrix form can be written as

$$\sum_{i=1}^{N}\left(\begin{bmatrix}\tilde{v}_{k,i}^{(0)} & \tilde{v}_{k,i}^{(1)} & \cdots & \tilde{v}_{k,i}^{(NMS-2)}\end{bmatrix}\begin{bmatrix} v_{l,i}^{(1)} \prod_{\substack{q=1\\(q,j)\neq(i,0)}}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \\ v_{l,i}^{(2)} \prod_{\substack{q=1\\(q,j)\neq(i,1)}}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \\ \vdots \\ v_{l,i}^{(NMS-1)} \prod_{\substack{q=1\\(q,j)\neq(i,NMS-2)}}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \end{bmatrix}\right) =$$

$$\sum_{i=1}^{N}\left(\begin{bmatrix}\tilde{v}_{k,i}^{(0)} & \tilde{v}_{k,i}^{(1)} & \cdots & \tilde{v}_{k,i}^{(NMS-2)}\end{bmatrix}\begin{bmatrix} 2\prod_{q=1}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \\ 2\prod_{q=1}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \\ \vdots \\ 2\prod_{q=1}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \end{bmatrix}\right) \tag{S34}$$

Following the same direction as in Section C, we enforce the above constraint for each sample. We have

$$\begin{bmatrix}\tilde{v}_{k,i}^{(0)} & \tilde{v}_{k,i}^{(1)} & \cdots & \tilde{v}_{k,i}^{(NMS-2)}\end{bmatrix}\begin{bmatrix} v_{l,i}^{(1)} \prod_{\substack{q=1\\(q,j)\neq(i,0)}}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \\ v_{l,i}^{(2)} \prod_{\substack{q=1\\(q,j)\neq(i,1)}}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \\ \vdots \\ v_{l,i}^{(NMS-1)} \prod_{\substack{q=1\\(q,j)\neq(i,NMS-2)}}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \end{bmatrix} = \begin{bmatrix}\tilde{v}_{k,i}^{(0)} & \tilde{v}_{k,i}^{(1)} & \cdots & \tilde{v}_{k,i}^{(NMS-2)}\end{bmatrix}\begin{bmatrix} 2\prod_{q=1}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \\ 2\prod_{q=1}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \\ \vdots \\ 2\prod_{q=1}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \end{bmatrix} \tag{S35}$$

Hence, for all values of k, we have the following equations,

$$\begin{bmatrix}\tilde{v}_{1,i}^{(0)} & \tilde{v}_{1,i}^{(1)} & \cdots & \tilde{v}_{1,i}^{(NMS-2)} \\ \tilde{v}_{2,i}^{(0)} & \tilde{v}_{2,i}^{(1)} & \cdots & \tilde{v}_{2,i}^{(NMS-2)} \\ \vdots & \vdots & \ddots & \vdots \\ \tilde{v}_{M,i}^{(0)} & \tilde{v}_{M,i}^{(1)} & \cdots & \tilde{v}_{M,i}^{(NMS-2)}\end{bmatrix}\left(\begin{bmatrix} v_{l,i}^{(1)} \prod_{\substack{q=1\\(q,j)\neq(i,0)}}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \\ v_{l,i}^{(2)} \prod_{\substack{q=1\\(q,j)\neq(i,1)}}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \\ \vdots \\ v_{l,i}^{(NMS-1)} \prod_{\substack{q=1\\(q,j)\neq(i,NMS-2)}}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \end{bmatrix} - \begin{bmatrix} 2\prod_{q=1}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \\ 2\prod_{q=1}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \\ \vdots \\ 2\prod_{q=1}^{N} \prod_{j=0}^{NMS-2} \sum_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \end{bmatrix}\right) = \mathbf{0}_{M\times 1}. \tag{S36}$$

If the matrix $\tilde{\mathbf{V}}_i$ given by

$$\tilde{\mathbf{V}}_i = \begin{bmatrix} \tilde{v}_{1,i}^{(0)} & \tilde{v}_{1,i}^{(1)} & \cdots & \tilde{v}_{1,i}^{(NMS-2)} \\ \tilde{v}_{2,i}^{(0)} & \tilde{v}_{2,i}^{(1)} & \cdots & \tilde{v}_{2,i}^{(NMS-2)} \\ \vdots & \vdots & \ddots & \vdots \\ \tilde{v}_{M,i}^{(0)} & \tilde{v}_{M,i}^{(1)} & \cdots & \tilde{v}_{M,i}^{(NMS-2)} \end{bmatrix} \tag{S37}$$

is full column rank, its null space is reduced to the singleton $\{0\}$. This matrix is column full rank when the number of column is less than the number of rows, i.e., $NMS-1<M$, which means $\mathbf{V}_i^T\mathbf{V}_i$ is invertible. Hence, by this assumption we have

$$\begin{bmatrix} v_{l,i}^{(1)} \prod\limits_{\substack{q=1 \\ (q,j)\neq(i,0)}}^{N} \prod\limits_{j=0}^{NMS-2} \sum\limits_{h=1}^{M} v_{h,q}^{(j)} p_{hl} \\ v_{l,i}^{(2)} \prod\limits_{\substack{q=1 \\ (q,j)\neq(i,1)}}^{N} \prod\limits_{j=0}^{NMS-2} \sum\limits_{h=1}^{M} v_{h,q}^{(j)} p_{hl} \\ \vdots \\ v_{l,i}^{(NMS-1)} \prod\limits_{\substack{q=1 \\ (q,j)\neq(i,NMS-2)}}^{N} \prod\limits_{j=0}^{NMS-2} \sum\limits_{h=1}^{M} v_{h,q}^{(j)} p_{hl} \end{bmatrix} - \begin{bmatrix} 2\prod\limits_{q=1}^{N} \prod\limits_{j=0}^{NMS-2} \sum\limits_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \\ 2\prod\limits_{q=1}^{N} \prod\limits_{j=0}^{NMS-2} \sum\limits_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \\ \vdots \\ 2\prod\limits_{q=1}^{N} \prod\limits_{j=0}^{NMS-2} \sum\limits_{h=1}^{M} \tilde{v}_{h,q}^{(j)} p_{hl} \end{bmatrix} = \mathbf{0}_{M\times 1}. \tag{S38}$$

Simplifying (S38), we have

$$\begin{bmatrix} v_{l,i}^{(1)} \\ v_{l,i}^{(2)} \\ \vdots \\ v_{l,i}^{(NMS-1)} \end{bmatrix} = \begin{bmatrix} 2\sum\limits_{h=1}^{M} \tilde{v}_{h,i}^{(0)} p_{hl} \\ 2\sum\limits_{h=1}^{M} \tilde{v}_{h,i}^{(1)} p_{hl} \\ \vdots \\ 2\sum\limits_{h=1}^{M} \tilde{v}_{h,i}^{(NMS-2)} p_{hl} \end{bmatrix} \Rightarrow$$

$$\begin{bmatrix} v_{l,i}^{(1)} \\ v_{l,i}^{(2)} \\ \vdots \\ v_{l,i}^{(NMS-1)} \end{bmatrix} = 2 \begin{bmatrix} \tilde{v}_{1,i}^{(0)} & \tilde{v}_{2,i}^{(0)} & \cdots & \tilde{v}_{M,i}^{(0)} \\ \tilde{v}_{1,i}^{(1)} & \tilde{v}_{2,i}^{(1)} & \cdots & \tilde{v}_{M,i}^{(1)} \\ \vdots & \vdots & \ddots & \vdots \\ \tilde{v}_{1,i}^{(NMS-2)} & \tilde{v}_{2,i}^{(NMS-2)} & \cdots & \tilde{v}_{M,i}^{(NMS-2)} \end{bmatrix} \begin{bmatrix} p_{1l} \\ p_{2l} \\ \vdots \\ p_{Ml} \end{bmatrix} \tag{S39}$$

This is the model we use for the Poisson observations of the cell proliferation Markov process.

Section E. Proof of Proposition 1

Starting from (S39), since a direction solution for the transition probabilities is not accessible in this case, we resort to an approximation. To this end, we use an one sample estimator for $\tilde{v}_{1,i}^{(0)}$ and replace it by $v_{1,i}^{(0)}$. We have

$$2\begin{bmatrix} v_{1,i}^{(0)} & v_{2,i}^{(0)} & \cdots & v_{M,i}^{(0)} \\ v_{1,i}^{(1)} & v_{2,i}^{(1)} & \cdots & v_{M,i}^{(1)} \\ \vdots & \vdots & \ddots & \vdots \\ v_{1,i}^{(NMS-2)} & v_{2,i}^{(NMS-2)} & \cdots & v_{M,i}^{(NMS-2)} \end{bmatrix}\begin{bmatrix} p_{1l} \\ p_{2l} \\ \vdots \\ p_{Ml} \end{bmatrix} = \begin{bmatrix} v_{l,i}^{(1)} \\ v_{l,i}^{(2)} \\ \vdots \\ v_{l,i}^{(NMS-1)} \end{bmatrix}. \tag{S40}$$

where, $i \in \{1, N\}$. The equation (S40) is satisfied for each sample, i, and cell type, l. The goal is set to find p_{hl}, $h, l \in [1, M]$, which fit the equations best in the minimum mean squared sense. We have

$$\hat{\mathbf{P}} = \arg\min_{\mathbf{P}} S(\mathbf{P}) \tag{S41-a}$$

$$\begin{aligned} &\text{s.t.} \\ &\text{for } \forall \;\; 1 \le h \le M, 1 \le l \le M, \\ &\quad 0 \le p_{hl} \le 1, \qquad \text{(S41-b)} \\ &\quad \sum_{l=1}^{M} p_{hl} = 1, \qquad \text{(S41-c)} \end{aligned}$$

where the objective function S is defined as

$$S(\mathbf{P}) = \sum_{l=1}^{M}\left(\sum_{i=1}^{N}\sum_{j=1}^{NMS-1}\left(v_{l,i}^{(j)} - 2\sum_{h=1}^{M}\tilde{v}_{h,i}^{(j-1)} p_{hl}\right)^2\right), \tag{S42}$$

The optimization problem in (S41) is convex, (cost function is quadratic and constraints are linear [2]). Using KKT (Karush–Kuhn–Tucker), the unconstrained solution for this problem is given by

$$S_U(\mathbf{P}) = \sum_{l=1}^{M}\left(S(\mathbf{P}_l) + \lambda_l\left(\sum_{j=1}^{M} p_{jl} - 1\right) + \sum_{j=1}^{M}\left(\lambda'_{jl} - \lambda''_{jl}\right) p_{jl},\right) \tag{S43}$$

where λ'_{jl}, λ''_{jl} and λ_l are Lagrange multipliers and $\mathbf{P}_l = [p_{1l} \;\; \cdots \;\; p_{Ml}]$. Computing the derivative of the cost function, with respect to p_{hl} and following some mathematical manipulations (similar to the Gaussian scenario), we have

$$\hat{\mathbf{P}}_l = 0.5\left(\left(\mathbf{V}_{:,1:N}^{(0:NMS-2)}\right)^{\dagger}\left(\mathbf{V}_{:,1:N}^{(0:NMS-2)}\right)\right)^{-1}\left(\mathbf{V}_{:,1:N}^{(0:NMS-2)}\right)^{\dagger}\mathbf{V}_{l,(1:N)}^{(1:NMS-1)} - \Lambda_l, \tag{S44}$$

where $\mathbf{V}_{:,1:N}^{(0:NMS-2)}$, $\mathbf{V}_{l,(1:N)}^{(1:NMS-1)}$ and Λ_l are defined in (S-13), (S-14) and (S-16). The above solution is obtained when the constraints $\left(0 \le p_{ij} \le 1\right)$ is assumed satisfied. However, if the obtained results violate these constraints, one should enforce them and solve the problem again (see Section B for details on handling this issue).

Section F. Proof of Proposition 2

Starting from (S39), since a direction solution for the transition probabilities is not accessible in this case, we resort to an alternative approximation in this Section. To this end, we consider the summation of (S39) over i and obtain

$$2\begin{bmatrix} \sum_{i=1}^{N}\tilde{v}_{1,i}^{(0)} & \cdots & \sum_{i=1}^{N}\tilde{v}_{M,i}^{(0)} \\ \vdots & \ddots & \vdots \\ \sum_{i=1}^{N}\tilde{v}_{1,i}^{(NMS-2)} & \cdots & \sum_{i=1}^{N}\tilde{v}_{M,i}^{(NMS-2)} \end{bmatrix}\begin{bmatrix} p_{1l} \\ \vdots \\ p_{Ml} \end{bmatrix} = \begin{bmatrix} \sum_{i=1}^{N}v_{l,i}^{(1)} \\ \vdots \\ \sum_{i=1}^{N}v_{l,i}^{(NMS-1)} \end{bmatrix}. \tag{S45}$$

Using the definition of a sample mean, and assuming $\frac{1}{N}\sum_{i=1}^{N}\tilde{v}_{l,i}^{k} = \frac{1}{N}\sum_{i=1}^{N}v_{l,i}^{k}$, we have

$$2\begin{bmatrix} \sum_{i=1}^{N}v_{1,i}^{(0)} & \cdots & \sum_{i=1}^{N}v_{M,i}^{(0)} \\ \vdots & \ddots & \vdots \\ \sum_{i=1}^{N}v_{1,i}^{(NMS-2)} & \cdots & \sum_{i=1}^{N}v_{M,i}^{(NMS-2)} \end{bmatrix}\begin{bmatrix} p_{1l} \\ \vdots \\ p_{Ml} \end{bmatrix} = \begin{bmatrix} \sum_{i=1}^{N}v_{l,i}^{(1)} \\ \vdots \\ \sum_{i=1}^{N}v_{l,i}^{(NMS-1)} \end{bmatrix}. \tag{S46}$$

If $NMS-1<M$, this linear algebraic system has an infinite number of solutions. If $NMS-1=M$, the above system of linear equations for p_{1l} has a single solution

$$\begin{bmatrix} p_{1l} \\ \vdots \\ p_{Ml} \end{bmatrix} = 0.5\begin{bmatrix} \sum_{i=1}^{N}v_{1,i}^{(0)} & \cdots & \sum_{i=1}^{N}v_{M,i}^{(0)} \\ \vdots & \ddots & \vdots \\ \sum_{i=1}^{N}v_{1,i}^{(NMS-2)} & \cdots & \sum_{i=1}^{N}v_{M,i}^{(NMS-2)} \end{bmatrix}^{-1}\begin{bmatrix} \sum_{i=1}^{N}v_{l,i}^{(1)} \\ \vdots \\ \sum_{i=1}^{N}v_{l,i}^{(NMS-1)} \end{bmatrix} \tag{S47}$$

If $NMS-1>M$, the solution in MSE sense is obtained with the same approach for the Gaussian distribution by replacing $\mathbf{V}_{:,1:N}^{(0:NMS-2)}$ and $\mathbf{V}_{l,(1:N)}^{(1:NMS-1)}$ in (S13) and (S14) by $\mathbf{\Sigma}_v$ and Ψ_l , which are described as follows

$$\mathbf{\Sigma}_v = \begin{bmatrix} \sum_{i=1}^{N}v_{1,i}^{(0)} & \cdots & \sum_{i=1}^{N}v_{M,i}^{(0)} \\ \vdots & \ddots & \vdots \\ \sum_{i=1}^{N}v_{1,i}^{(NMS-2)} & \cdots & \sum_{i=1}^{N}v_{M,i}^{(NMS-2)} \end{bmatrix}. \tag{S48}$$

$$\Psi_l = \begin{bmatrix} \sum_{i=1}^{N}v_{l,i}^{(1)} & \cdots & \sum_{i=1}^{N}v_{l,i}^{(NMS-1)} \end{bmatrix}. \tag{S49}$$

The above solution is obtained when the constraints $\left(0 \leq p_{ij} \leq 1\right)$ is assumed satisfied. However, if the obtained results violate these constraints, one should enforce them and solve the problem again (see Section B for details on handling this issue).

References

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