

The diagram illustrates a cell-based signaling model. On the left, a cell is shown with an intracellular space containing several components: a nucleus (N, blue square), a Golgi apparatus (G, orange square), an endoplasmic reticulum (EA, purple square), and an endosome (EI, pink square). A nuclear pore (NP, purple circle) is also present. The cell is surrounded by an extracellular space. On the right, another cell is shown, with an inset graph displaying 'Molecule Count' versus 'Time' for various signaling molecules. The graph shows multiple colored lines representing different molecule counts over time. The cell-cell interactions are categorized into three types: Autocrine Signaling (green dashed arrows), Paracrine Signaling (blue dashed arrows), and Membrane Exchange (orange dashed arrows). The extracellular space is labeled 'Extracellular Space' and the intracellular space is labeled 'Intracellular Space'.

B)

The diagram illustrates the proposed framework for inferring cell-cell signaling, showing the flow from simulation to posterior estimation and proposal distribution.

Simulation and Pattern Score Calculation:

- CELL SCALE:** Molecule Count vs. Time. Plots show the dynamics of signaling molecules (NANOG, GATA6, FGF4) under two conditions: **CELL-CELL SIGNALING OFF** (red arrows) and **CELL-CELL SIGNALING ON** (cyan arrows).
- TISSUE SCALE:** Cell Position vs. Cell Count. Plots show the spatial distribution of cells (EPI, PRE, UND) under the same two conditions.
- Pattern Score:** Marginal Pattern Score 1 (red) and Joint Pattern Score (cyan) are calculated from the tissue-scale data.

ANN Training Dataset: The dataset is used to train the ANN, which outputs the **Posterior Distribution**.

Posterior Distribution Estimation: The **Posterior Distribution** is estimated using the **SNPE** (Sequential Neural Posterior Estimation) method, which takes the **Pattern Score** as input.

Proposal Distribution Estimation: The **Posterior Distribution** is combined with the **Prior** distribution (represented by a heatmap) using a **Mixer** to produce the **Next-Round Proposal Distribution**.

Meta-Analysis: The **Meta Score** is calculated from the **Posterior Distribution** and used to refine the **Proposal Distribution**.

Next-Round Proposal Distribution: The final output of the framework, which is used to generate the next round of simulation data.