

Same-Cell Biology: Beyond the Single-Cell Snapshot

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Single-cell technologies transformed biology by revealing the molecular, and in particular the transcriptional, diversity of individual cells, uncovering how much cells differed even within populations once assumed to be uniform. Spatial technologies added another axis: where those cells sit within their tissue.

Yet neither advance changed the underlying limitation: both approaches still require destroying the cell to measure it. You can see diversity, and you can see location, but not what happens to any individual cell next.

That is the new same-cell frontier: understanding what happens to the same living cell over time, and why.

Dr. Beyer obtained his PhD in Cell Biology at ETH Zurich. After a postdoctoral fellowship at the LTRI in Toronto, he joined ETH Zurich as junior group leader. There, he combined his expertise in cell biology, cell signaling and embryonic stem cells with genome engineering using the CRISPR/Cas9 technology.

At Cytosurge, Dr. Beyer uses his skills to identify and develop applications for the FluidFM OMNIUM.



Article Content

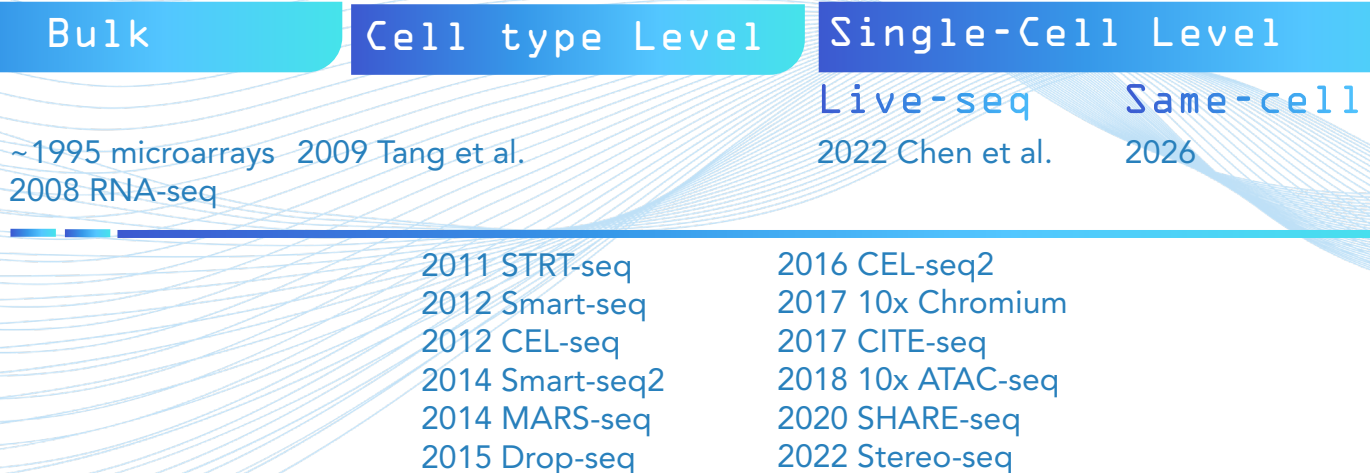
- "01 · The revolution that changed biology" on page 2
- "02 · The missing dimension: Biology is dynamic" on page 3
- "03 · The causality gap" on page 5
- "04 · Defining Same-Cell Biology" on page 6
- "05 · Why this matters for drug discovery" on page 7
- "06 · The enabling technology" on page 9
- "07 · The future we are building toward" on page 10
- "External Sources (alphabetical order)" on page 12

01 • The revolution that changed biology

For most of my career, I thought the hardest problem in biology was resolution: first seeing cells clearly enough under the microscope to tell them apart by shape and appearance. Then resolving their transcriptomes finely enough to do the same, distinguishing one cell type from another by its expression profile and building maps detailed enough to surface rare populations that bulk measurements had averaged into silence.

But the question that kept coming back was more fundamental: **why do individual cells respond so differently to the very same stimulus depending on the context?**

Part of the answer is structural. Bulk measurement has a longer history than people often remember. Microarrays gave biology its first genome-wide transcriptomes in the mid-1990s, averaging expression across thousands or millions of pooled cells into a single profile. RNA sequencing arrived in 2008, replacing hybridization with direct sequencing but keeping the same bulk logic: one sample, one averaged readout. Rare populations vanished into the mean. **Transient states vanished with them.**



The single-cell revolution delivered on all of that. In 2009, Tang and colleagues shattered the limitations of bulk experiments, sequencing the transcriptome of a single mouse oocyte and individual blastomeres from four-cell embryos (Tang et al., *Nature Methods*, 2009).

Over the roughly fifteen years since, single-cell RNA sequencing technology, in its many forms, revealed cellular heterogeneity that had been invisible for decades. The atlas projects enabled the cataloging of cell types and states across tissues with a precision that population biology could not approach. That achievement is real. It changed what biology could ask and what medicine could see.

But I have come to see it as a first act, not a conclusion.

The single-cell era revealed what cells are. It built extraordinary maps of cellular states. What it was never designed to explain is the question that mattered more to me: why two cells that have apparently the same phenotype, that sit in the same (transcriptional) cluster, express the same markers, can meet the same signal and answer it differently.

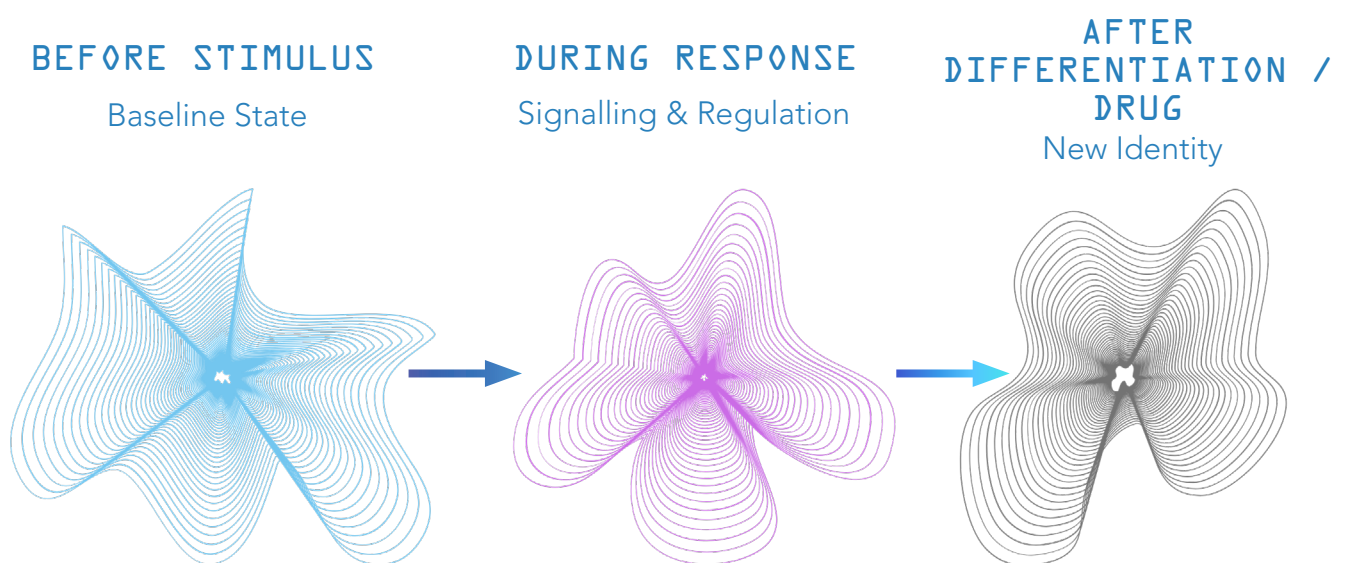
Answering this requires a fundamental shift, from measuring different cells at a single point in time to following the same cell through change.

02 • The missing dimension: Biology is dynamic

A cell is not a static object. It is a living system with unprecedented plasticity traversing time.

Its molecular state at any moment is the product of its history, the signals it received, the perturbations it survived, the regulatory decisions that preceded it.

The questions that follow are the ones now driving drug discovery. Why did this cell, identical-looking to its neighbors at the start of the experiment, respond differently to the drug? Why did this iPSC veer into an off-target differentiation fate? Why does this tumor cell resist the combination therapy while its sister cells die? Why did the genome edit produce an effect here but not there?

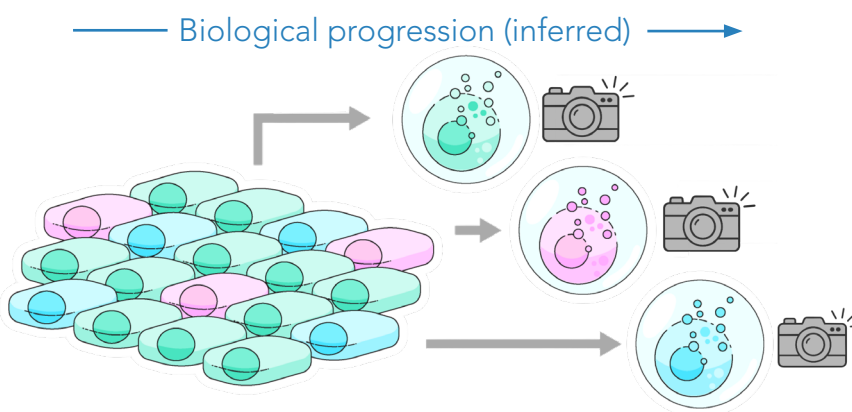


These are not questions about cellular identity. They are questions about cellular trajectory: how a particular cell becomes something different, and why. Answering them requires observing the same cell across time. It requires connecting what the cell was before the intervention to what it became afterward.

Standard single-cell technologies suffer from a fundamental, structural paradox: the cells must be lysed and destroyed to be read, capturing only a static snapshot of a cell at the moment it ceased to exist. Consequently, measuring real-time, continuous cellular dynamics has remained impossible. The wider scientific community explicitly acknowledges this bottleneck, as noted by Dong et al. in *Nature Methods* (2023): “To generate causal assertions about the effect of a perturbation on the transcriptional state of a given cell, we ideally would measure the same cell both before and after a perturbation. However, the process of obtaining transcript measurements from single cells is destructive, and an individual cell may be measured only once.” While computational frameworks offer sophisticated statistical workarounds to infer these counterfactual states, the underlying constraint remains: as long as molecular profiling relies on destructive endpoint measurements, causal understanding of transcriptional dynamics depends on inference rather than direct, same-cell observation.

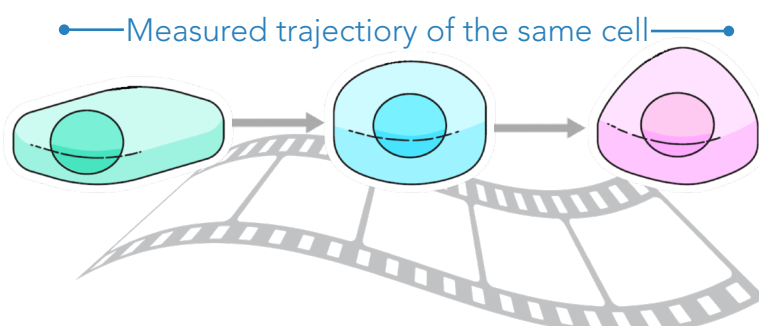
Inference is powerful. Pseudotime analyses have produced genuine biological insight. But inference is not the same as measurement. When you reconstruct a cellular trajectory from a population of individually destroyed cells, you are describing what cells like this one probably did. **We are not measuring the cell’s actual path; we are estimating the most likely one.**

A snapshot shows where and what a cell is.
It rarely reveals how it got there, where it will go next,
or what caused it to adopt that particular
fate or trajectory.



TRADITIONAL SINGLE-CELL APPROACH

Many cells, one time point each. Heterogeneity is measured, trajectories are inferred.



SAME-CELL BIOLOGY

Once cell, many time points. Dynamics are measured. Cause and effect become testable.

03 • The causality gap

This distinction, correlation versus causation, inference versus measurement, sits at the center of where biology and pharma are hitting a structural ceiling.

The field has accumulated an extraordinary wealth of single-cell data, generating an abundance of associations between molecular signatures and cellular phenotypes. Yet correlation is not causation. While high-throughput functional genomics platforms like Perturb-seq have successfully introduced interventional screens to bridge this gap, their causal power remains bound to population-level averages. Because perturbations are randomly assigned across a pooled population, comparing the average transcriptional state of perturbed cells to that of controls yields a statistically valid causal estimate, in the same logic as a randomized controlled trial. **But because the transcriptomic readout inherently destroys the cell, each cell can be measured only once, in either its perturbed or its unperturbed state, never both.** The population-level causal effect is therefore built by comparing the average of one group of cells to the average of a different group, not by tracking any single cell across its actual before-and-after trajectory.

We are left with a fundamental limitation in resolution: we can observe true causality across a pooled population, but we cannot capture the true counterfactual state of an individual cell. Establishing per-cell causality requires a different experimental paradigm entirely.

To move beyond statistical inference and population averaging, researchers must be able to intervene at the single-cell level, observe the functional outcome within that exact same cellular boundary, and directly connect the two, capturing the true 'before' and 'after' states of the identical living cell.

The modeling community is confronting a related limitation from another direction.

A 2026 analysis of virtual cell models found that scaling data and model capacity fails to solve perturbation prediction, because the causal mechanism linking perturbation to response itself changes across biological contexts. The authors connect this explicitly to causal transportability theory, which formalizes when knowledge learned in one domain can be applied to another, and conclude that the field faces a “causal transport problem” that cannot be solved by accumulating more data from the same distributions (Dibaeinia et al., *bioRxiv* 2026).

This finding points to a different but related gap in how the field generates its training data in the first place. Virtual cell models, like Perturb-seq before them, are trained overwhelmingly on destructive endpoint measurements: different cells, snapshotted once, then pooled into population averages. That data regime cannot represent the actual within-cell transition from baseline to response, only its population-level approximation, and that is a structural constraint that no increase in model scale or dataset size removes.

True longitudinal single-cell data, in which the same living cell is measured, perturbed, and measured again, addresses this specific input: it supplies the individual causal transition rather than an inferred population proxy.

Whether that measurement resolution is sufficient on its own to resolve transportability across contexts remains an open question; what it does resolve is the narrower, prior problem of what the training data represents in the first place.

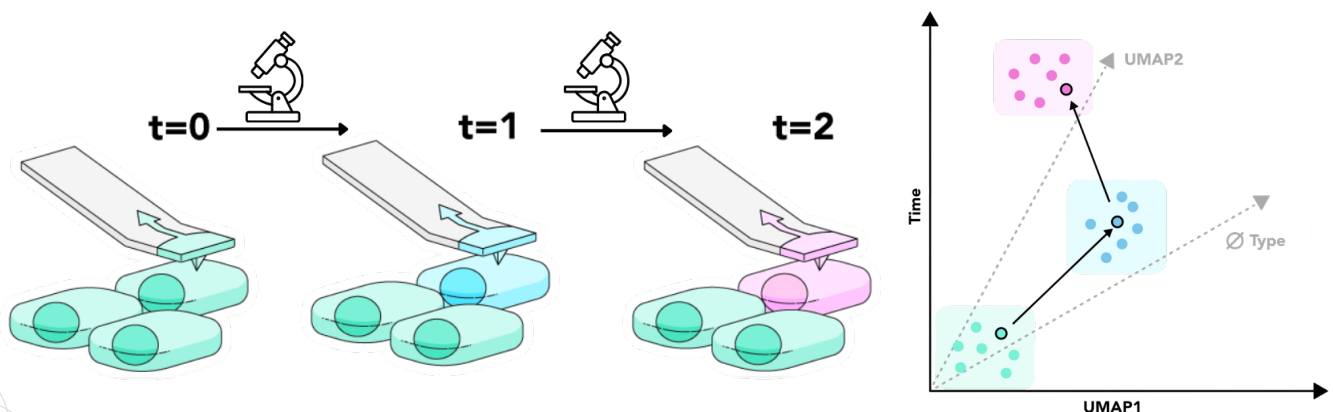
04 • Defining Same-Cell Biology

Same-Cell Biology is the paradigm built to close the causality gap by enabling access to a single, identified living cell with nanoscale precision and control to keep the cell alive.

Traditional high-dimensional molecular profiling in biology hits the same wall: to measure a cell, you have to kill it, so you never see what it would have become. In genome engineering, conventional delivery methods perturb the cell beyond the intended genetic edit, affecting viability, fitness, or cellular state. This represents another constraint that Same-Cell Biology can help address and that we will explore in a future *CYTOSURGE PERSPECTIVES* article.

The underlying technological capability is precise access to an individual living cell while preserving its viability.

Applied to single-cell analysis, this enables live-cell sequencing (Live-seq). This means reading a cell's molecular state, perturbing it, and reading the same cell again. The connection between intervention, molecular change, and subsequent outcome is not reconstructed from population averages; it is directly observed in one individual entity. The cell is its own baseline, before and after.



Follow the exact same cell through experimental interventions. Biopsy the cell, apply a stimulus or drug, and biopsy it again to capture its true biological trajectory.

The contrast is worth stating clearly. Single-cell biology resolves which cell. Spatial biology resolves where that cell is located. Same-Cell Biology resolves what happened to that same cell over time. It adds the dimension the first two paradigms, for reasons built into their measurement architecture, could not supply: continuity.

The same cell, before and after.
Cause and effect, not inference.

05 • Why this matters for drug discovery

Pharma R&D's practical stakes sit earlier in the pipeline than most assume: lack of efficacy is the largest single cause of clinical failure, at 40 to 50 percent, versus 30 percent for toxicity and 10 to 15 percent for poor drug-like properties (Sun et al., *Acta Pharmaceutica Sinica B*, 2022). Efficacy failure is usually a target and mechanism problem: the assumed causal driver of disease was wrong. Industry postmortems agree: "the right target" is one of few technical determinants of success (Cook et al., *Nature Reviews Drug Discovery*, 2014).

The bottleneck is target validation, not engineering or toxicology.

The clearest evidence comes from human germline genetics: mechanisms with germline support, inherited variants, have 2.6 times the probability of clinical success (Minikel et al., *Nature*, 2024), building on earlier findings that such support roughly doubled approval rates (Nelson et al., *Nature Genetics*, 2015; King et al., *PLOS Genetics*, 2019).

This evidence is causal by construction: a variant is fixed before disease onset, independent of the disease it later explains, so it cannot be its consequence. In oncology, a second, separate class, somatic driver mutations, BRAF V600E, EGFR L858R, BCR-ABL, are not inherited but arise early within the disease itself, so germline logic cannot apply; their causal status instead rests on direct experiments, isogenic knock-in/knockout and oncogene-addiction rescue, showing the mutation is necessary and sufficient to drive and sustain the transformed phenotype. Minikel et al. report this separately (relative success 2.3 for somatic versus 2.6 for germline): comparable strength, via intervention rather than inheritance.

Same-cell measurement offers a third route, structurally closer to the somatic model than the germline one: neither relies on inheritance being independent of environment; both establish causality through direct intervention and observation within one biological unit, a clone for somatic, a single cell for us. Population readouts only show that perturbed cells differ from unperturbed ones: a correlation.

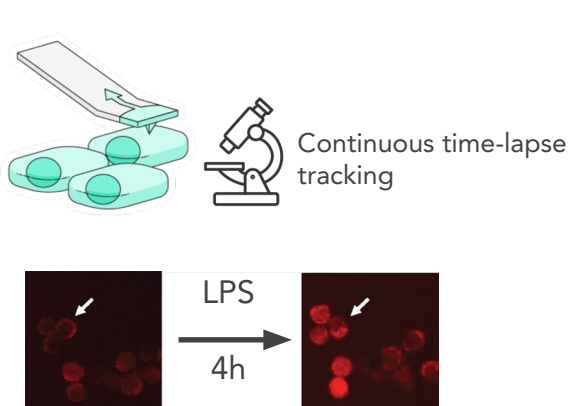
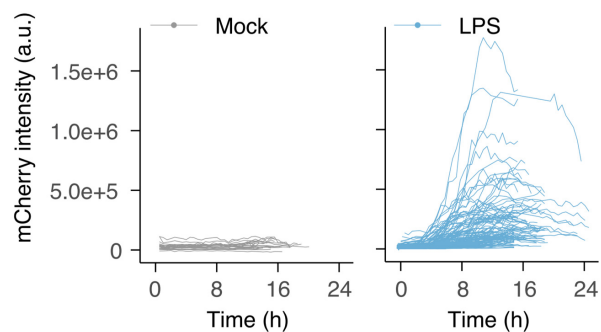
Same-cell measurement shows that this cell changed after this perturbation, one cell's before-and-after state, causal for the same reason a driver-mutation knock-in is: the "before" state is fixed by direct measurement prior to intervention, not inferred, so it cannot be explained away as a consequence of the response itself.

It extends to any target and cell system, including most with no germline variant or driver mutation.

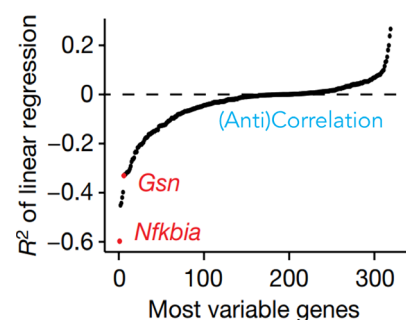
The founding demonstration of Live-seq cytoplasmic biopsy, the method that makes same-cell molecular readouts possible, showed a concrete example of what this reveals. In LPS-stimulated macrophages, the basal level of *Nfkb*, measured before LPS stimulation, predicted the magnitude of the subsequent TNF response in that same cell (Chen et al., *Nature*, 2022).

That relationship is invisible to endpoint measurement. When you profile LPS-treated cells only at the endpoint, *Nfkb* and TNF appear positively correlated, because both are induced together once the cell responds to the stimulus. But the endpoint correlation and the same-cell relationship are not two conflicting answers to the same question; they are answers to two different questions. The endpoint snapshot captures co-induction: how much two genes move together after a cell has already responded. The same-cell recording captures prediction: whether a cell's state before the perturbation forecasts the size of its response afterward. Collapse both into a single snapshot and the second question disappears, not because the endpoint measurement is wrong, but because it was never built to answer it.

State predicts fate, but only when you measure the state before the perturbation and the fate after, in the same cell.



Predicting the rate of *Tnf*-mCherry increase using Live-seq data



Left, top: LPS-stimulated macrophages exhibit heterogeneous NF- κ B activity. Left, bottom: Cytoplasmic biopsies recover the pre-stimulus transcriptome and link it to the post-stimulus phenotype.

Adapted from Chen et al., *Nature* (2022)

Looking ahead, the same paired, same-cell data that resolves target validation and mechanism questions today is also the substrate for the predictive models Cytosurge is building.

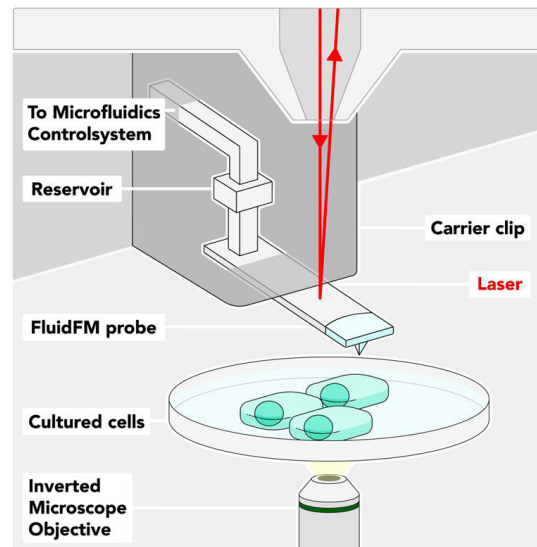
As this causal data accumulates at scale, models trained on it are intended to make target identification faster and more reliable earlier in the pipeline, before a program commits to costly downstream development. That capability is on our roadmap; it is not a product available today.

06 • The enabling technology

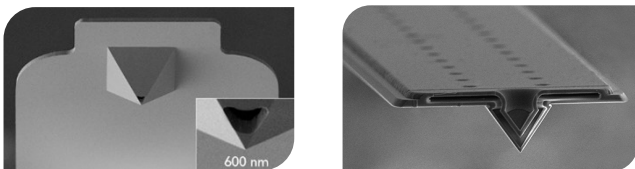
At the foundation of Same-Cell Biology is one technological capability: gentle access to a living cell with nanoscale precision, while keeping it viable. The FluidFM® Nanosyringe is a hollow microcantilever with an aperture of approximately 550 nanometers, operating under nanonewton-scale force feedback. It gently pierces the plasma membrane of a living cell that is selected by live-cell microscopy. For Live-seq, it withdraws on the order of a few picoliters of cytoplasm. Then it retracts. The membrane reseals. The cell lives on.



The FluidFM® technology is commercialized as the OMNIUM, our Same-Cell Biology platform, operated via the proprietary Arya software.



Schematic illustration of the FluidFM® technology.



Scanning electron microscopy (SEM) micrographs of a FluidFM® Nanosyringe (left), with the fluidic channel opened for illustrative purposes (right).



Fluidic Force Microscopy
2026 Nature Reviews Methods
Primers.

These experiments can be run in-house on the FluidFM® OMNIUM platform, which provides the instrument, workflows, and integration with live-cell microscopy and downstream sequencing chemistry. Alternatively, live-cell sequencing can be accessed through Cytosurge's Causal Insights service, providing the same experimental approach without the need for an in-house platform.

07 • The future we are building toward

I do not think the single-cell era ends. The atlas data is real and valuable. Maps of cellular states across tissues and conditions provide a foundation that biological research will build on for decades to come. Profiling ten million cells in a single run answers a different and legitimate question: what is the diversity of cell states across a tissue or population, and the platforms that do this at scale are impressive. They are not competitors to Same-Cell Biology; they are prior paradigms answering prior questions. The questions they could not ask belong to the regime I am describing here.

What changes is which questions you bring to which architecture. If your question is about which states exist in a tissue, an atlas is the right instrument. If your question is about what happened to a specific cell after a specific intervention, what it was before, what it became, and what connects those two facts, you need a recording, not a snapshot.

We are in the early phase of what this data class makes possible. The field is beginning to explore it from more than one direction. Marcuccio et al. (*Science Advances*, 2024) used a nanopipette platform that performs paired, non-destructive extractions from the same glioblastoma cell and its progeny. They sampled it before and after chemotherapy and radiotherapy, over a 72-hour window, and found that treatment appears to select for more transcriptionally stable cells.

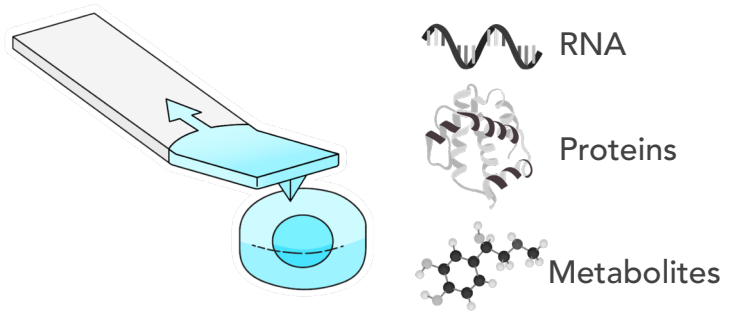
The platform reaches that result by a different physical route than ours. It positions its pipette using ion-current feedback, not the force feedback FluidFM relies on to sense and gently control contact with the cell. Its injection step is also performed manually, under microscope guidance, rather than under closed-loop control, making this related work, not an interchangeable method.

That an independent group is pursuing same-cell longitudinal transcriptomics at all is the more important point. It turns this from one company's claim into an emerging paradigm. And it is worth being explicit about what that paradigm is for.

Paired same-cell data functions first as ground truth and evaluation substrate for predictive models, and only second as training corpus.

That is what should make it matter to a modeler, not only to a methods developer.

Even the best-resourced scaling efforts illustrate the limit rather than close it. Xaira's X-Cell, a 4.9-billion-parameter diffusion model trained on 25.6 million perturbed single-cell transcriptomes across 16 cellular contexts, is the largest causal perturbation model built to date (Wang et al., *bioRxiv*, 2026). Every cell in that dataset is measured once, after a fixed perturbation, then destroyed. Scale and context diversity solve one part of the problem. They do not solve the part that requires watching the same cell twice.



Seamlessly integrate with high-end analytical workflows:

- Transcriptome: Dynamic gene activity across time.
- Proteome: Mass spectrometry on whole samples.
- Metabolome: Real-time metabolic conditions in living cells

Biology's ultimate goal has always been to understand cause and effect in living systems. Why do cells behave as they do? What makes them change? What happens when we intervene precisely and observe what follows?

Same-Cell Biology does not close every gap in biology. But for the specific question in front of you, it gets you closer. Instead of inferring a pattern across a population of different cells, we follow one living cell through a defined intervention: measure it, perturb it, then measure it again, all without ever letting the cell go. That moves us beyond snapshots to the biological equivalent of a movie: a direct before-and-after of the same living cell.

The next era of biology will not only ask which cells exist. It will ask what happens when we perturb them or their context.

That is the question we built for.

Tobias Beyer, PhD
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External Sources (alphabetical order)

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