

# Autological Oncology — A Functional Model of Structural Evolution in Cellular Systems

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## Abstract

This paper proposes a measurable framework for structural reflexivity in biological systems.

It extends the functional law of *Autological Recursion*

$$\Psi = \frac{\partial S}{\partial R}$$

to cancer biology, interpreting cancer as a condition in which regulatory structures (S) lose sensitivity to recurrent environmental or intracellular perturbations (R).

The resulting metric,  $\Psi_{\text{eff}}$ , quantifies the degree to which gene-regulatory syntax changes per unit repetition.

Together with  $L_{\text{eff}} = \Delta E / \Delta S$  (energetic load) and C (coherence of identity), it forms a diagnostic triad for cellular adaptability.

The framework is not a therapy claim but a testable scaffold.

It outlines experimental proxies derived from existing single-cell and epigenomic assays, a simulation pipeline for hypothesis generation, and an ethical roadmap for reversible validation in organoid models.

## 0 • Background

Adaptive systems maintain homeostasis by modifying the rules that govern their own operations.

Kognetik formalizes this meta-adaptation as

$$\Psi = \partial S / \partial R,$$

where  $R$  denotes repeated operations and  $S$  the structure that shapes them.

High  $\Psi \rightarrow$  rule responsiveness; low  $\Psi \rightarrow$  rigid recursion.

Cancer is modeled as  $\Psi \approx 0$ , a loop that reproduces without learning.

## 1 • Operationalization

Symbol	Definition	Observable proxy	Data source
$R$	Repetition / stress cycle	experimental perturbation schedule	lab metadata
$\Delta R$	change per cycle	normalized stress magnitude	protocol
$S$	gene-regulatory syntax	GRN topology + RNA motifs + chromatin state	scRNA-seq + ATAC-seq
$\Delta S$	structural change	difference in GRN edge weights + motif accessibility	computational
$\Psi_{\text{eff}}$	functional reflexivity	$\ \Delta S\  / (\ \Delta R\  + \varepsilon)$	derived
$L_{\text{eff}}$	energetic load	ATP use / $\Delta S$ or #genes per $\Delta S$	metabolomics + transcriptomics
$C$	coherence	stability of lineage / marker profile	imaging + IHC

### Interpretation

- $\Psi_{\text{eff}} \uparrow \rightarrow$  adaptive rule revision
- $L_{\text{eff}} \downarrow \rightarrow$  efficient integration
- $C$  stable  $\rightarrow$  preserved identity

## 2 · Experimental Roadmap

### Phase 1 — RNA Reflexivity Assay

Goal: detect transcriptional rule adaptation under repeated stress.

- Model: tumour organoids or immortalized cell lines
- Perturbation: 6 × hypoxia/reoxygenation cycles
- Measure: scRNA-seq each cycle → network inference →  $\Delta S$ ,  $\Delta R$  →  $\Psi_{\text{eff}}$  trajectory
- Expected pattern: healthy  $\Psi_{\text{eff}} > 0$  ; malignant  $\Psi_{\text{eff}} \approx 0$ .

### Phase 2 — Epigenetic Feedback Test

Add CUT&Tag/ATAC to capture chromatin dynamics.

Checks whether structural changes ( $\Delta S$ ) correlate with energy shifts ( $\Delta E$ ) and transcriptional recovery.

### Phase 3 — Rule Perturbation Test

Introduce reversible CRISPRi/a or dCas9-p300/TET edits on motifs identified in Phase 1.

- Design: ABAB (on/off) for 3 cycles each.
- Criteria:  $\Psi_{\text{eff}} \uparrow \geq 15\%$ ,  $L_{\text{eff}} \downarrow \geq 10\%$ , C stable  $\pm 5\%$ .
- Safety: off-target  $< 1\%$ , viability  $> 90\%$ .

## 3 · Computational Framework

A lightweight simulator complements wet-lab data.

for cycle in stress\_schedule:

```
 $\Delta R = \text{norm}(\text{stress}[c+1] - \text{stress}[c])$ 
```

```
GRN_new = infer_network(scRNA[c])
```

```
 $\Delta S = \text{distance}(\text{GRN\_new}, \text{GRN\_prev})$ 
```

```
 $\Psi_{\text{eff}} = \Delta S / (\Delta R + 1e-12)$ 
```

```
 $L_{\text{eff}} = \text{energy\_estimate}(\text{GRN\_new}) / (\Delta S + 1e-12)$ 
```

```
record( $\Psi_{\text{eff}}$ ,  $L_{\text{eff}}$ )
```

Outputs a trajectory of  $\Psi_{\text{eff}}$  and  $L_{\text{eff}}$  per cycle.

Model parameters calibrated with organoid data establish predictive validity.

## 4 • Interpretation Matrix

Observation	Structural meaning	Clinical implication
$\Psi_{\text{eff}} \uparrow, L_{\text{eff}} \downarrow, C \approx \text{const}$	Adaptive recursion	responsive / reversible state
$\Psi_{\text{eff}} \approx 0, L_{\text{eff}} \uparrow$	Rigid recursion	refractory / terminal loop
$\Psi_{\text{eff}} \downarrow$ with $\text{RDI} > 1$	Overshooting recursion	unstable feedback; halt edits

Key outcome:  $\Psi_{\text{eff}}$  distinguishes *learning* vs *locked* cellular dynamics.

## 5 • RNA Networks as Structural Syntax

RNA constitutes the operational grammar between genome and phenotype. Transcripts, splicing variants, and small RNAs regulate the same processes that produce them — a biochemical recursion.

$$\Psi_{RNA} = \frac{\|\Delta S_{RNA}\|}{\|\Delta R_{RNA}\| + \varepsilon}.$$

Proxies:

- $\Delta R_{RNA}$ : RNA velocity vectors per stress cycle.
- $\Delta S_{RNA}$ : change in miRNA/lncRNA network topology.
- $\Psi_{RNA} \uparrow \rightarrow$  functional adaptability;  $\Psi_{RNA} \approx 0 \rightarrow$  syntactic freeze.

This allows autological parameters to be extracted directly from RNA-seq data without altering DNA.

## 6 • Ethical and Methodological Governance

1. Ex-vivo first. No in-vivo edits until proxies validated.
2. Reversibility only. Use CRISPRi/a or epigenetic modifiers, never nuclease-based cuts.
3. RDI tripwire. Abort if rate ( $\rho$ ) > stabilization latency ( $\lambda$ ) or  $\Psi \uparrow$  with  $L \uparrow$ .
4. Transparency. Pre-registration, open code, publication of null results.

5. Autological Ethics. Oversight functions as higher-order recursion — the rule that governs rule-change.

## **7 • Limitations**

1.  $\Psi$  eff as proxy, not constant.  
The parameter represents a functional approximation; precision depends on data resolution and network-inference reliability.
2. Noise and identifiability.  
Gene-regulatory networks reconstructed from single-cell data are underdetermined; bootstrapping or Bayesian ensemble averaging is required.
3. Tumour heterogeneity.  
Subclonal variability may mask  $\Psi$ -trends; lineage-barcoding or single-cell tracking recommended.
4. Energetic measurement limits.  
ATP-cost estimation remains indirect;  $\Delta E$  should be treated as a relative rather than absolute metric.
5. No therapeutic claim.  
Framework restricted to quantifying structural learning capacity, not proposing patient interventions.

## **8 • Discussion — From Concept to Measurement**

### **8.1 Why $\Psi$ is useful even when approximate**

Many accepted biological descriptors (e.g., tumour heterogeneity index, EMT-score, entropy of chromatin accessibility) are derived constructs.

$\Psi$  eff offers a unified gradient of structural responsiveness, linking transcriptional, epigenetic, and metabolic adaptation under a single formalism.

### **8.2 Relation to existing theories**

- Free-Energy Principle (Friston 2010):  $\Psi$  measures structural sensitivity to prediction error rather than its minimisation.
- Autopoiesis (Varela & Maturana 1980):  $\Psi$  quantifies the self-modification rate of autopoietic organisation.
- Systems Oncology: extends network-entropy metrics toward functional recursion.

### 8.3 Potential applications

- Quantify cellular plasticity under therapy.
- Predict drug-resistance trajectories.
- Detect irreversible loop states ( $\Psi \approx 0$ ) → flag for non-adaptive lesions.
- Map reprogramming efficiency in induced differentiation.

### 8.4 Practical next steps

1. Release an open source  $\Psi$ -analysis pipeline (Python + R).
2. Reanalyse public scRNA/ATAC datasets for  $\Psi$  eff trends.
3. Publish Pilot Dataset (3 cell lines × 6 cycles) with full code.
4. Invite collaboration for Organoid-based validation.

## 9 • Conclusion

Cancer can be read as a failure of structural recursion — a system that repeats without revising.

Autological Oncology reframes this as a measurable property rather than a metaphor:

$$\Psi_{eff} = \frac{\|\Delta S\|}{\|\Delta R\|}$$

approximates how sensitively regulation changes under repetition.

If  $\Psi_{eff} > 0$  and  $L_{eff} \downarrow$ , the cell learns; if  $\Psi \approx 0$  and  $L \uparrow$ , it loops.

The framework thus supplies:

- a quantitative language for adaptive capacity,
- an ethical model for minimal-risk rule intervention,
- and a bridge between systems biology and recursive cognition.

Evolution learns by rewriting its own syntax.

Disease begins where that recursion stops.

Measuring  $\Psi$  is measuring the point where life forgets to learn.\*\*

## Appendix A • Notation

Symbol Description

R	repetition / perturbation vector
$\Delta R$	change per cycle
S	structural syntax (GRN + epigenetic architecture)
$\Delta S$	measured structural shift
$\Psi_{\text{eff}}$	functional reflexivity index
$L_{\text{eff}}$	energetic load
C	phenotypic coherence
$\rho / \lambda$	rate / stabilisation latency
RDI	rate-delay instability ( $\rho / \lambda$ )
$\Delta E$	energy differential

## Appendix B • Pseudocode

# Simplified  $\Psi_{\text{eff}}$  computation from single-cell data

for cycle in stress\_schedule:

$\Delta R = \text{norm}(\text{stress}[c+1] - \text{stress}[c])$

    GRN\_new = infer\_network(scRNA[c])

$\Delta S = \text{network\_distance}(\text{GRN\_new}, \text{GRN\_prev})$

$\Psi_{\text{eff}} = \Delta S / (\Delta R + 1e-12)$

$L_{\text{eff}} = \text{estimate\_ATP}(\text{GRN\_new}) / (\Delta S + 1e-12)$

    if RDI(GRN\_new) > 1 or C\_drop(GRN\_new):

        break # safety stop

    record\_metrics( $\Psi_{\text{eff}}$ ,  $L_{\text{eff}}$ , C)

## Appendix C · Ethical Protocol

1. All experiments ex-vivo until proxy metrics validated.
2. Use reversible CRISPRi/a or epigenetic modifiers only.
3. Pre-registration and open code release mandatory.
4. Immediate halt for runaway recursion ( $\rho > \lambda$ ) or identity collapse.
5. Full reporting of negative results.

## Appendix D · $\Psi$ -Analysis Notebook (Prototype)

### Purpose:

Provide a minimal, reproducible script for estimating structural reflexivity ( $\Psi_{\text{eff}}$ ) and energetic load ( $L_{\text{eff}}$ ) from existing single-cell RNA + ATAC datasets.

### D.1 Required Inputs

Dataset	Description	Example Source
rna_matrix	scRNA-seq counts (genes × cells) across stress cycles	GEO / ArrayExpress
atac_matrix	ATAC-seq peak accessibility	GEO / ENCODE
stress_vector	Normalised perturbation intensity per cycle	lab metadata

### D.2 Core Procedure (pseudocode)

```
import numpy as np, pandas as pd
```

```
# 1. Load and normalise data
```

```
rna = load_scRNA_matrices(path="data/rna_matrix/")
```

```
atac = load_ATAC_matrices(path="data/atac_matrix/")
```

```
stress = np.array([0,1,2,3,4,5,6]) # e.g., hypoxia cycles
```

```
# 2. Infer network structure per cycle (e.g., correlation or GENIE3)
```

```
def infer_GRN(expr):
```



```

return compute_network(expr, method="GENIE3")

# 3. Structural change  $\Delta S$  between cycles
def network_distance(G1, G2):
    return np.linalg.norm(G1 - G2)

# 4. Compute  $\Psi_{\text{eff}}$  and  $L_{\text{eff}}$ 
 $\Psi_{\text{eff}}$ ,  $L_{\text{eff}}$  = [], []
for c in range(len(stress)-1):
     $\Delta R$  = abs(stress[c+1]-stress[c])
    GRN_new = infer_GRN(rna[c])
     $\Delta S$  = network_distance(GRN_new, infer_GRN(rna[c-1]))
    energy = estimate_ATP_usage(rna[c])    # optional proxy
     $\Psi_{\text{eff}}$ .append( $\Delta S$  / ( $\Delta R$  + 1e-12))
     $L_{\text{eff}}$ .append(energy / ( $\Delta S$  + 1e-12))

# 5. Visualisation
plot_timecourse(stress[1:],  $\Psi_{\text{eff}}$ , ylabel=" $\Psi_{\text{eff}}$  (Structural Reflexivity)")
plot_correlation( $\Psi_{\text{eff}}$ ,  $L_{\text{eff}}$ , xlabel=" $\Psi_{\text{eff}}$ ", ylabel=" $L_{\text{eff}}$ ")

save_results({" $\Psi_{\text{eff}}$ ": $\Psi_{\text{eff}}$ , " $L_{\text{eff}}$ ": $L_{\text{eff}}$ }, "results/psi_analysis.csv")

```

### D.3 Output Metrics

Variable	Meaning	Expected Pattern
$\Psi_{\text{eff}}$	Rule adaptivity per cycle	↑ in responsive cells, ≈ 0 in rigid cells
$L_{\text{eff}}$	Energy cost of regulation	↓ if adaptive integration
<b><math>\Psi_{\text{eff}} \times L_{\text{eff}}</math> plot</b> Reflexivity vs efficiency map clusters → phenotypic classes		

#### D.4 Interpretation

- A positive  $\Psi_{\text{eff}}$  trajectory (monotonic  $\uparrow$ ) with falling  $L_{\text{eff}} \Rightarrow$  adaptive recursion.
- Flat or negative  $\Psi_{\text{eff}} \Rightarrow$  maladaptive loop (cancer-like rigidity).
- Variance across cells = heterogeneity index ( $\Delta\Psi$  spread).

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#### Author Note

This document is intended as an exploratory and testable theoretical scaffold.

$\Psi$ ,  $L$ , and  $C$  are data-derived proxies; no therapeutic claims are made.

The purpose is to stimulate empirical evaluation of structural reflexivity in living systems.