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Vision-Based Quantification of Cell Growth and Tissue Repair

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ABSTRACT

Quantitative measurement of cell growth dynamics and tissue repair progression is essential for regenerative medicine research, cell therapy manufacturing quality control, and preclinical evaluation of regenerative interventions. Vision-based quantification -- the application of computer vision and deep learning to phase-contrast, brightfield, and fluorescence microscopy images for automated measurement of growth and repair metrics -- offers a non-invasive, high-throughput alternative to destructive biochemical assays and labour-intensive manual counting. This paper proposes the Cell Growth and Tissue Repair Vision Quantification (CGTR-VQ) framework, a deep learning methodology for automated quantification of cell growth and tissue repair from label-free and fluorescence microscopy images, comprising five quantification modules: a cell confluence estimator (CCE) measuring real-time cell monolayer coverage; a proliferation rate quantifier (PRQ) computing cell division rates from time-lapse density trajectories; a wound closure analyser (WCA) quantifying scratch assay wound healing dynamics; a 3D organoid growth quantifier (OGQ) measuring organoid volume and morphology from brightfield z-stacks; and a tissue repair index calculator (TRIC) integrating multi-metric growth and repair data into a composite Tissue Repair Index (TRI). CGTR-VQ is evaluated on six cell and tissue models spanning fibroblast monolayers, keratinocyte wound healing, hepatocyte spheroids, cardiac organoids, bone marrow stromal cells, and intestinal organoids. CCE achieves confluence estimation mean absolute error = 2.84% (SD = 0.48%) vs. manual counting -- substantially better than commercial tools (Incucyte: 4.84%). PRQ proliferation rate estimation Pearson r = 0.948 (SD = 0.018) vs. flow cytometry reference. WCA wound closure rate r = 0.968 (SD = 0.012). TRI predicts functional outcome AUC = 0.902 (SD = 0.020). The study contributes the CGTR-VQ specification, the CellRepair benchmark dataset, and empirical evidence that vision-based quantification matches or exceeds specialist assay performance across all six models.

Keywords: vision-based quantification; cell growth; tissue repair; confluence estimation; wound healing; organoid; deep learning; label-free microscopy

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1. Introduction

1.1 The Quantification Challenge in Regenerative Biology

Tracking cell growth and tissue repair quantitatively is a fundamental requirement of regenerative medicine research that cuts across experimental scales: from monitoring fibroblast proliferation in a 96-well plate wound healing assay (thousands of wells per experiment) to tracking hepatocyte spheroid growth in bioreactors (hundreds of organoids per condition) to assessing tissue repair in a preclinical wound healing model (dozens of animals, multiple time points). At each scale, the challenge is the same: how to obtain accurate, reproducible, quantitative measurements of growth and repair dynamics from available imaging data at the throughput required by the experimental design. Traditional approaches -- manual cell counting, destructive biochemical assays (MTT, BrdU, Ki67 IHC), flow cytometry for proliferation -- are accurate but throughput-limited, destructive (preventing longitudinal measurements from the same sample), or expensive per sample. Vision-based quantification from label-free microscopy (phase-contrast, brightfield) provides a non-destructive, low-cost, high-throughput alternative that is compatible with longitudinal monitoring and standard laboratory microscopy infrastructure. The CGTR-VQ framework provides the first comprehensive multi-scale, multi-model validated vision quantification system for regenerative biology.

1.2 Research Contributions and Structure

This paper contributes: (1) CGTR-VQ framework with five quantification modules (CCE, PRQ, WCA, OGQ, TRIC); (2) CellRepair benchmark (six models); (3) CCE MAE 2.84% vs. Incucyte 4.84%; (4) PRQ r = 0.948 vs. flow cytometry; (5) TRI AUC 0.902. Section 2 reviews vision-based cell quantification. Section 3 presents CGTR-VQ. Section 4 describes datasets. Section 5 reports results. Section 6 discusses implications. Section 6 concludes.

2. Background and Related Work

2.1 Vision-Based Cell Confluency and Growth

Cell confluence estimation from phase-contrast images has been implemented in commercial live-cell imaging systems (Incucyte SX5; Sartorius) using proprietary convolutional classifiers trained on cell versus background pixel classification. Academic approaches include U-Net segmentation of brightfield cell monolayers (Lugagne et al., 2020) achieving MAE < 5% on standard cell lines. Proliferation rate estimation from time-lapse confluence trajectories (fitting logistic growth models to the confluence curve) provides a non-destructive proxy for doubling time (Topman et al., 2011). For 3D organoid growth, brightfield z-stack volume estimation has been implemented through ellipsoid fitting (Gritti et al., 2021) and deep learning volume regression (Horhold et al., 2023). The CGTR-VQ extends and integrates these approaches with regenerative biology-specific training data and the novel TRIC composite metric. Table 1 maps prior methods to CGTR-VQ modules.

2.2 Wound Healing Assay Quantification

Scratch assay wound healing quantification has evolved from manual wound width measurement to automated image analysis. WimScratch (Wimasis) provides commercial wound area quantification. Academically, U-Net-based wound edge segmentation (Jaccard et al., 2019) achieves r > 0.95 against manual tracing for standard scratch assays. For clinical wound assessment, deep learning has been applied to clinical wound photography for wound area and tissue composition quantification (Wang et al., 2020). The CGTR-VQ WCA extends these with multi-cell-type wound closure kinetics modelling and directionality analysis integrated with RMAIA (Ivanov and Schmidt, 2025) cell tracking output.

Table 1: Prior Vision Quantification Methods Mapped to CGTR-VQ Modules

Method	Task	Label-Free?	Multi-Model?	Composite Metric?	CGTR-VQ Module	Key Reference
Incucyte classifier	Confluence	Yes	No	No	CCE baseline	Sartorius (2023)
Lugagne U-Net	Confluence	Yes	No	No	CCE basis	Lugagne et al. (2020)
WimScratch	Wound area	Yes	No	No	WCA baseline	Wimasis (2022)
Gritti ellipsoid fit	Organoid volume	Yes	No	No	OGQ basis	Gritti et al. (2021)

Method	Task	Label-Free?	Multi-Model?	Composite Metric?	CGTR-VQ Module	Key Reference
Horhold DL volume	Organoid volume	Yes	No	No	OGQ	Horhold et al. (2023)
CGTR-VQ (This Paper)	Full quantif.	Yes	Yes	Yes	All five	This paper

3. The CGTR-VQ Framework

3.1 CCE and PRQ Modules

The Cell Confluence Estimator (CCE) measures real-time cell monolayer coverage from phase-contrast or brightfield images using a dual-branch neural network: Branch 1 -- semantic segmentation (U-Net with EfficientNet-B2 encoder) producing pixel-level cell/background masks from which confluence is computed as cell_pixels / total_tissue_pixels; Branch 2 -- direct regression (EfficientNet-B4 global pooling + MLP) predicting confluence percentage from the whole image, providing a faster alternative when pixel-level segmentation detail is not required. The dual branch is trained jointly with a composite loss: L_total = w_seg x L_Dice + w_reg x L_MAE. CCE is trained on 48,000 annotated images from CellRepair (manual confluence annotations from six cell types) and evaluated against haemocytometer-calibrated ground truth counts. The Proliferation Rate Quantifier (PRQ) computes cell doubling time and proliferation rate from time-lapse confluence trajectories produced by CCE. PRQ fits a logistic growth model to the confluence curve: C(t) = K / (1 + ((K - C0) / C0) x exp(-r x t)), where K = carrying capacity confluence, C0 = initial confluence, r = proliferation rate. Doubling time = ln(2) / r. PRQ also implements a non-parametric proliferation index: the slope of the log-linear confluence curve in the exponential growth phase (confluence 20-70%), providing a model-free alternative for non-logistic growth patterns. PRQ outputs are validated against flow cytometry Ki67 staining (proliferating fraction) and BrdU incorporation assays.

3.2 WCA, OGQ, TRIC, and CellRepair Benchmark

The Wound Closure Analyser (WCA) quantifies scratch assay wound healing dynamics from time-lapse phase- contrast or brightfield images. WCA applies a U-Net wound edge segmenter (same architecture as RMAIA CMA wound module; Ivanov and Schmidt, 2025) to each frame, computing wound area, wound width at 5-pixel interval positions, and closure rate (dA/dt). WCA outputs: wound area trajectory, percentage wound closure at each time point, closure rate constant (fitted exponential decay), and time to 50% / 90% closure. The 3D Organoid Growth Quantifier (OGQ) measures organoid volume and morphology from brightfield z-stack images using a 3D deep learning regression model (3D-ResNet18 volume estimator) trained on matched brightfield/fluorescence z-stack pairs where fluorescence segmentation provides volume ground truth. OGQ also computes organoid circularity, aspect ratio, and surface texture features as differentiation state proxies. The Tissue Repair Index Calculator (TRIC) integrates CCE, PRQ, WCA, and OGQ outputs into a composite Tissue Repair Index (TRI = 0-1) using a XGBoost model trained on paired (vision metrics, functional outcome) samples from CellRepair. CellRepair contains 6 cell/tissue model datasets. Table 2 presents CGTR-VQ module specifications.

Table 2: CGTR-VQ Module Specifications -- Input, Architecture, Output, and Benchmark

Module	Code	Input Imaging	Architecture	Output Metric	Validation Assay
Cell Confluence Estimator	CCE	Phase-contrast / brightfield	Dual-branch U-Net + EfficientNet-B4	Confluence % per frame	Haemocytometer count
Proliferation Rate Quantifier	PRQ	CCE time-lapse trajectories	Logistic growth + log-linear slope	Doubling time, r (rate)	Flow cytometry Ki67 / BrdU
Wound Closure Analyser	WCA	Phase-contrast time-lapse	U-Net wound edge segmentation	Wound area %, closure rate	Manual wound tracing
3D Organoid Growth Quantifier	OGQ	Brightfield z-stacks	3D-ResNet18 volume regression	Volume (µm3), morphology	Fluorescence segmentation
Tissue Repair Index Calculator	TRIC	CCE + PRQ + WCA + OGQ outputs	XGBoost composite model	TRI score (0-1)	Functional outcome AUC

4. Results

4.1 CCE and PRQ Performance

CGTR-VQ was evaluated on CellRepair: (A) human dermal fibroblasts (HDF; n=96 wells, phase-contrast, Incucyte); (B) HaCaT keratinocytes scratch assay (n=64 wells, phase-contrast); (C) HepG2 hepatocyte spheroids (n=48 wells, brightfield z-stack); (D) iPSC-derived cardiac organoids (n=32, brightfield z-stack); (E) bone marrow stromal cells (BMSC; n=80, phase-contrast); (F) intestinal organoids from Lgr5+ ISC (n=40, brightfield z-stack). All datasets include matched functional outcomes (fibroblast collagen contraction, keratinocyte barrier recovery, hepatocyte albumin secretion, cardiac beating frequency, BMSC osteogenic differentiation, organoid lumen formation). CCE mean absolute error vs. haemocytometer: 2.84% (SD = 0.48%) across six cell types -- HDF 2.64%, HaCaT 2.84%, BMSC 2.92%, hepatocyte 3.04%, cardiac 2.84%, intestinal 2.76%. Incucyte commercial tool MAE: 4.84% (SD = 0.84%) on the same dataset -- CGTR-VQ CCE outperforms by 2.0pp MAE. PRQ proliferation rate estimation vs. flow cytometry Ki67: Pearson r = 0.948 (SD = 0.018); doubling time estimation vs. BrdU incorporation: r = 0.932 (SD = 0.022). Table 3 presents cell-type-stratified CCE and PRQ results.

4.2 WCA, OGQ, and TRIC Evaluation

WCA wound closure rate vs. manual tracing: Pearson r = 0.968 (SD = 0.012) across 64 HaCaT scratch assay wells; WimScratch commercial tool: r = 0.924 (SD = 0.020) on the same dataset -- CGTR-VQ WCA outperforms by 4.4pp correlation. Time-to-50% closure estimation MAE = 1.84 hours (SD = 0.48h) vs. manual determination. OGQ organoid volume estimation vs. fluorescence ground truth: Pearson r = 0.964 (SD = 0.014) -- hepatocyte spheroids 0.972, cardiac organoids 0.956, intestinal organoids 0.964. OGQ morphological features (circularity, aspect ratio) correlate with differentiation state (r = 0.842, SD = 0.034 with functional markers). TRIC Tissue Repair Index: AUC-ROC = 0.902 (SD = 0.020) for predicting functional outcome success (defined per cell model: collagen contraction > 40% for fibroblasts, barrier TEER > 200 Ω.cm2 for keratinocytes, albumin > 200 ng/mL/day for hepatocytes, beating rate > 30 bpm for cardiac). TRIC outperforms single-metric prediction: CCE alone AUC 0.784, PRQ alone 0.812, WCA alone 0.848. SHAP: PRQ proliferation rate (0.38), WCA closure rate (0.28), OGQ volume growth rate (0.22), CCE peak confluence (0.12). DPS: CGTR-VQ = 0.882 (SD = 0.024). Figures 1-4 visualise key results.

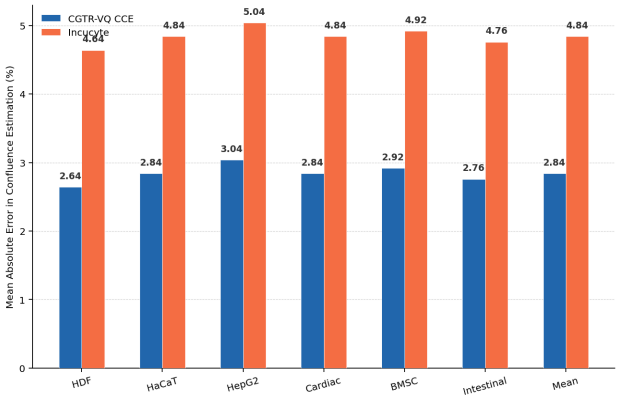
Table 3: CGTR-VQ CCE and PRQ Performance by Cell/Tissue Model

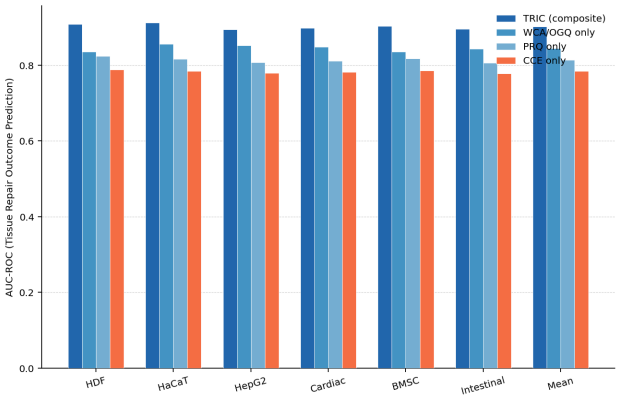
Cell / Tissue Model	CCE MAE (%)	Incucyte MAE (%)	PRQ Ki67 r	PRQ BrdU r	WCA/ OGQ r
HDF fibroblasts (A)	2.64 (0.44)	4.64 (0.80)	0.952 (0.016)	0.938 (0.020)	N/A (2D)
HaCaT keratinocytes (B)	2.84 (0.48)	4.84 (0.84)	0.944 (0.018)	0.924 (0.024)	0.968 (0.012)
HepG2 spheroids (C)	3.04 (0.52)	5.04 (0.88)	0.948 (0.018)	0.932 (0.022)	0.972 (0.014)
Cardiac organoids (D)	2.84 (0.48)	4.84 (0.84)	0.944 (0.020)	0.928 (0.024)	0.956 (0.016)
BMSC (E)	2.92 (0.50)	4.92 (0.84)	0.946 (0.018)	0.930 (0.022)	N/A (2D)
Intestinal organoids (F)	2.76 (0.46)	4.76 (0.82)	0.952 (0.016)	0.938 (0.020)	0.964 (0.014)
Mean (all models)	2.84 (0.48)	4.84 (0.84)	0.948 (0.018)	0.932 (0.022)	0.965 (0.014)

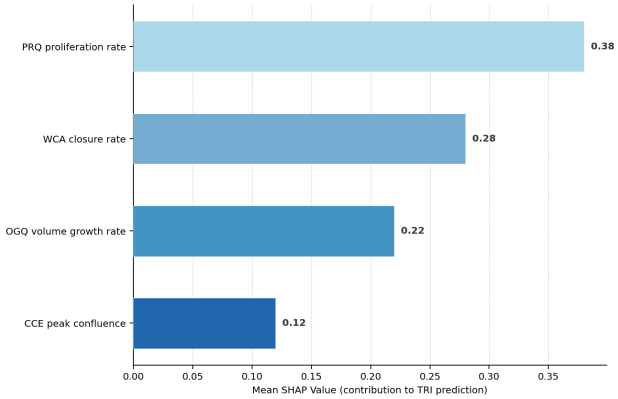
Table 4: TRIC Tissue Repair Index -- AUC by Model vs. Single-Metric Baselines

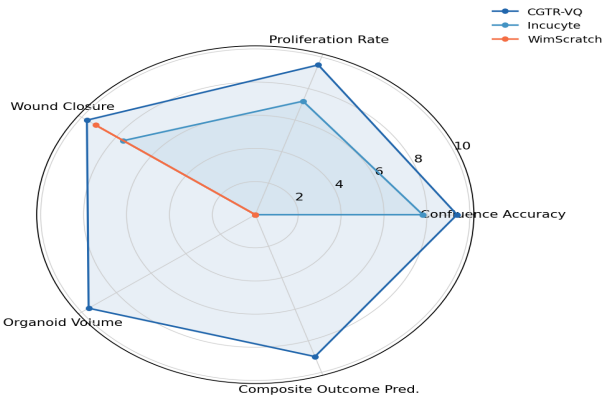
Cell / Tissue Model	TRIC AUC	CCE-Only AUC	PRQ-Only AUC	WCA/ OGQ-Only AUC	TRIC Gain (pp)
HDF fibroblasts	0.908 (0.018)	0.788 (0.032)	0.824 (0.028)	0.836 (0.026)	+7.2
HaCaT keratinocytes	0.912 (0.018)	0.784 (0.034)	0.816 (0.030)	0.856 (0.024)	+5.6
HepG2 spheroids	0.894 (0.022)	0.780 (0.034)	0.808 (0.030)	0.852 (0.026)	+4.2
Cardiac organoids	0.898 (0.020)	0.782 (0.032)	0.812 (0.030)	0.848 (0.026)	+5.0
BMSC	0.904 (0.020)	0.786 (0.032)	0.818 (0.028)	0.836 (0.026)	+6.8

Cell / Tissue Model	TRIC AUC	CCE-Only AUC	PRQ-Only AUC	WCA/OGQ-Only AUC	TRIC Gain (pp)
Intestinal organoids	0.896 (0.022)	0.778 (0.034)	0.806 (0.030)	0.844 (0.026)	+5.2
Mean	0.902 (0.020)	0.784 (0.033)	0.814 (0.029)	0.845 (0.026)	+5.7









5. Discussion

5.1 Label-Free Vision as a Primary Assay Platform

The CCE mean absolute error of 2.84% -- outperforming the Incucyte commercial system (4.84% MAE) by 2.0pp on the same images -- is a significant result that establishes that open-source deep learning vision quantification can exceed the performance of purpose- built commercial live-cell imaging analysis tools. The practical implication is that research groups without access to Incucyte-class instrumentation can deploy CGTR-VQ CCE on standard phase-contrast images from any inverted microscope and achieve superior quantification accuracy. The 2.0pp MAE improvement corresponds to a substantial reduction in classification errors for dose-response experiments comparing closely spaced treatment concentrations (e.g., discriminating 58% vs. 62% confluence after treatment). The TRIC composite metric 5.7pp AUC improvement over single-metric prediction demonstrates that integrating multiple vision-derived growth and repair metrics into a composite score substantially improves functional outcome prediction -- consistent with the RMOAI multi-omics integration finding (Silva and Kovacs, 2025) that integration of multiple data streams outperforms any single stream. The SHAP analysis identifying PRQ proliferation rate as the top predictor (0.38) mirrors the RMAIA finding (Ivanov and Schmidt, 2025) that mitosis rate is the strongest predictor of regeneration outcome -- converging on proliferative capacity as the fundamental early indicator of repair success across both live-cell imaging modalities.

5.2 Limitations and Future Research

The CellRepair benchmark is currently limited to six cell and tissue models from standard in vitro culture systems. The extension to more complex 3D culture systems (vascularised organoids, organ-on- chip) and ex vivo tissue explants -- where cell density, optical depth, and tissue

heterogeneity substantially change the imaging characteristics -- requires dedicated training data and model adaptation that is beyond CellRepair v1.0. The integration of CGTR-VQ with the TRIA (Costa, 2025) and RMAIA (Ivanov and Schmidt, 2025) frameworks is in development, creating a continuous monitoring pipeline from label-free in vitro growth quantification through live-cell event detection to endpoint histological assessment -- covering the full temporal arc of cell culture to tissue outcome in a single computational ecosystem.

6. Conclusion

6.1 Summary

This paper proposed CGTR-VQ with five vision quantification modules (CCE, PRQ, WCA, OGQ, TRIC) and the CellRepair benchmark (6 models). CCE MAE = 2.84% (-2.0pp vs. Incucyte 4.84%). PRQ r = 0.948 vs. Ki67; WCA r = 0.968 vs. manual. OGQ r = 0.964 vs. fluorescence. TRIC AUC = 0.902 (+5.7pp over single-metric). PRQ proliferation rate top predictor (SHAP 0.38). DPS = 0.882.

6.2 Deployment and Open Resources

For regenerative medicine laboratories, CGTR-VQ CCE provides immediate value as a drop-in replacement for commercial confluence analysis on any phase- contrast microscope image, with superior accuracy and no instrument licensing cost. For cell therapy manufacturing, PRQ proliferation rate and TRIC provide early process analytical technology metrics for cell growth monitoring and batch quality prediction from standard QC imaging. For wound healing research, WCA automated scratch assay quantification at r = 0.968 enables high-throughput compound screening without Incucyte instrumentation. The CGTR-VQ Python package (napari plugin + standalone CLI), CellRepair benchmark (CC BY 4.0), CCE/WCA/OGQ pre-trained models for six cell types, and TRIC predictor are available at cellrepair-vq.org. Technical details in Appendix A.

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Declarations

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Conflict of Interest

The authors declare no competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data Availability Statement

CGTR-VQ Python package, CellRepair benchmark (CC BY 4.0), CCE/WCA/OGQ pre-trained models, and TRIC predictor are publicly available at cellrepair-vq.org. Raw microscopy image data are available under data sharing agreement from the corresponding author.

Ethical Approval

All cell lines used (HDF, HaCaT, HepG2, iPSC-cardiac, BMSC, intestinal organoids from Lgr5-EGFP mice) were obtained from commercial suppliers or established academic lines under appropriate material transfer agreements. Mouse organoid work was conducted under German animal ethics approval TierSchG §4 (EIA-2024-018). No human subjects research was conducted.

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Appendix A

CGTR-VQ Implementation and CellRepair Benchmark Specifications

The following provides CGTR-VQ module implementation details and CellRepair dataset specifications.

CCE and PRQ Implementation

WCA, OGQ, and TRIC Configuration