# How Cells Feel

## Modelling Interactions of Cells with Their Environment

Directed Reading Program

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# Why Mechanotransduction?

- **Cells are not passive**

  They actively sense and respond to the physical properties of their environment (e.g., ECM) — stiffness, geometry, etc.

- **Mechanical cues drive cell fate**

  Mesenchymal stem cells — multipotent progenitor cells that can differentiate into a variety of cell types — follow different lineages depending on substrate stiffness: soft substrates promote neurogenesis (the formation of brain tissue), while stiff substrates promote osteogenesis (the formation of bone).

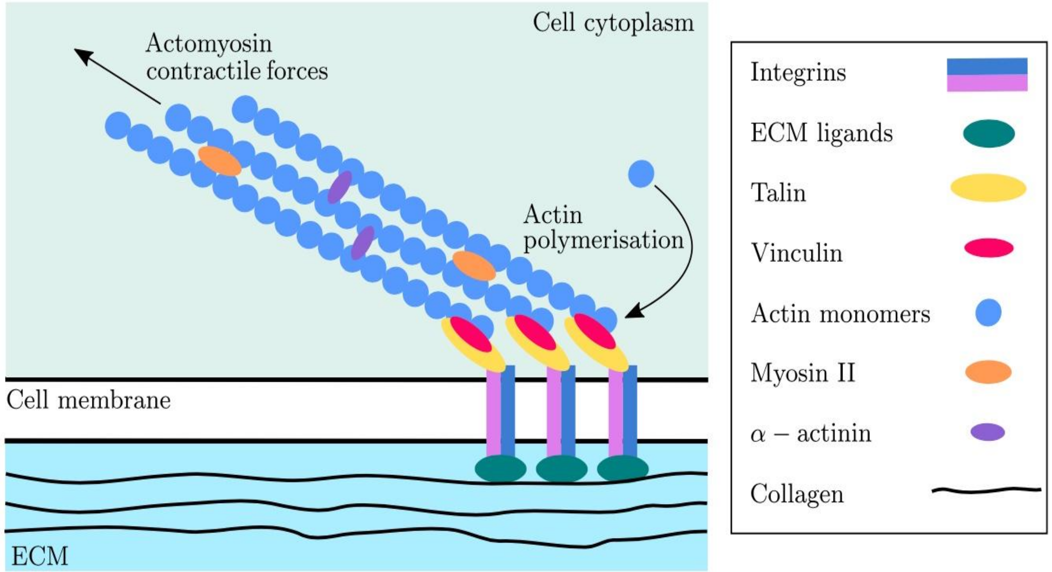
- **Clinical relevance**

  Mechanosensing is also implicated in fibrosis, cancer metastasis, and cardiovascular disease. Understanding the signaling pathways opens doors for targeted therapies.

- **Mathematical modelling**

  The coupled biochemical-mechanical system is complex, and reduced systems consisting of only ODEs have been shown to capture must of the observed behavior of cell-substrate interaction.

# The Cell–ECM Interface



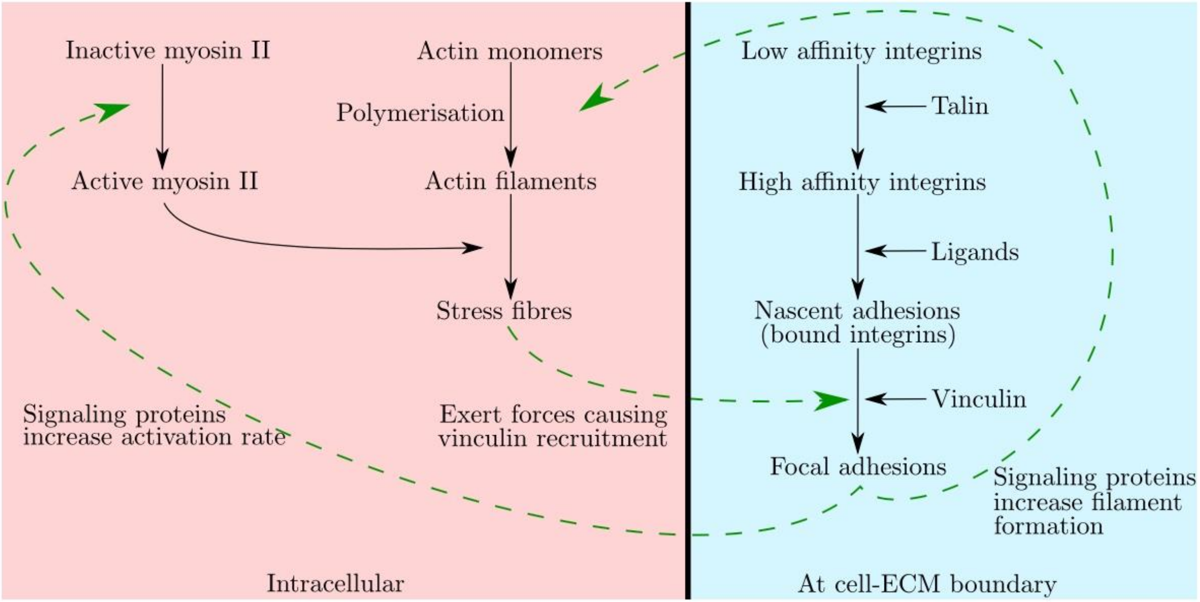

Integrins bind ECM ligands to form nascent adhesions

Adhesions mature into focal adhesions via stress fibre–mediated forces

Rho/ROCK signalling activates myosin II and suppresses actin depolymerisation

Positive feedback: FAs → ROCK → stress fibres → more FAs

# The Reaction Network




### Intracellular

Actin monomers polymerise into filaments, then cross-link with myosin II to form contractile stress fibres.

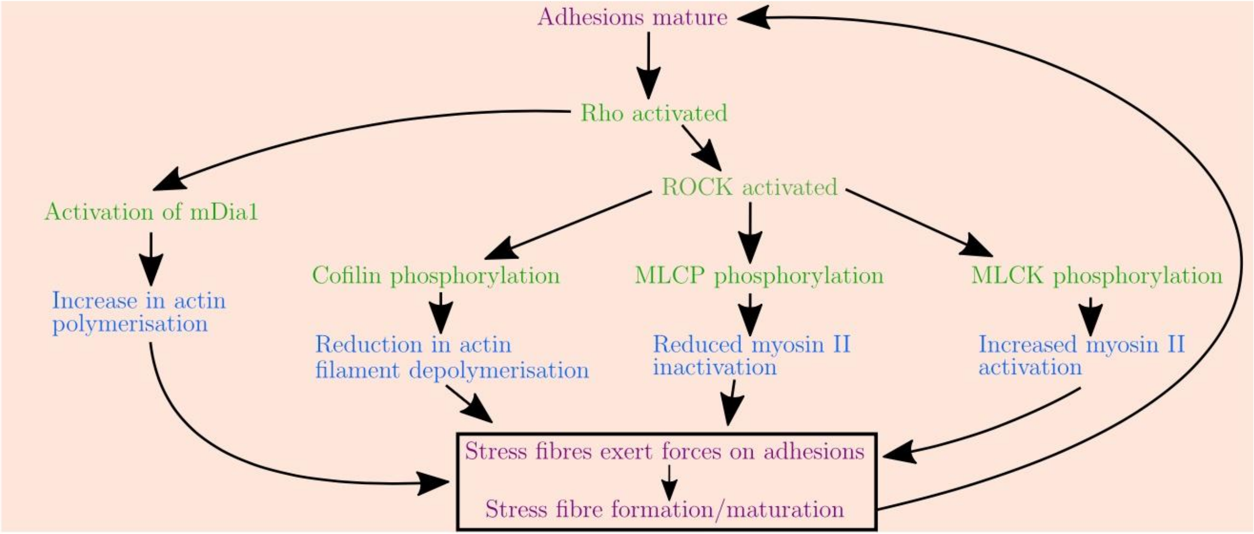
### Cell–ECM Boundary

Integrins switch affinity, bind ligands to form nascent adhesions, then mature into focal adhesions via vinculin recruitment.

### Feedback (dashed)

Signalling proteins couple both sides: SFs drive adhesion maturation, and adhesions drive signalling.

# The Signaling Cascade




### How ROCK drives the system

1. Adhesion maturation activates Rho → ROCK
2. ROCK phosphorylates cofilin: reduces F-actin depolymerization
3. ROCK phosphorylates MLCP: reduces myosin inactivation
4. ROCK phosphorylates MLCK: increases myosin activation
5. mDia1 activation: increases actin polymerization rate
6. Net result: more stress fibers → more adhesion maturation

This cascade is captured by a system of 18 coupled ODEs, where each arrow represents a reaction rate that feeds back into the system.

Since stretch and forces are not explicitly modelled, adhesion maturation is instead driven by stress fibers concentration as a mechanical proxy.

# The Mathematical Model

18 coupled ODEs describing:

- **Cytoskeleton (3 eqs)**
  G-actin, F-actin, VSFs
- **Myosin II (2 eqs)**
  Inactive & activated myosin
- **Adhesion (5 eqs)**
  Free, high-affinity, bound integrins, FAs, substrate sites, ligands
- **Signaling (8 eqs)**
  ROCK, MLCP, MLCK, cofilin (each active/inactive)

$$A + B \underset{k^-}{\overset{k^+}{\rightleftharpoons}} C$$

$$\boxed{\frac{dC_A}{dt} = -\underbrace{k^+ \cdot C_A \cdot C_B}_{\text{consumed by binding}} + \underbrace{k^- \cdot C_C}_{\text{recovered by dissociation}}}$$

# How Biology Becomes Equations

Each biochemical reaction follows **mass-action kinetics**: the rate of a reaction is proportional to the concentrations of its reactants.

## General Form

Consider a reversible binding reaction:

$$A + B \underset{k^-}{\overset{k^+}{\rightleftharpoons}} C$$

The ODE for species $A$ is:

$$\boxed{\frac{dC_A}{dt} = -\underbrace{k^+ \cdot C_A \cdot C_B}_{\text{consumed by binding}} + \underbrace{k^- \cdot C_C}_{\text{recovered by dissociation}}}$$

## Example — Actin Polymerisation

G-actin (free monomers, $c_G$) polymerises onto F-actin filaments and is recovered when filaments depolymerise or stress fibres disassemble:

$$\boxed{\frac{dc_G}{dt} = \underbrace{-k_p^+ \, c_G \, (n_B + n_A)}_{\substack{\text{polymerisation at barbed} \\ \text{and pointed ends}}} + \underbrace{k_p^- \, c_F}_{\substack{\text{F-actin} \\ \text{depolymerisation}}} + \underbrace{k_m^- \, c_{S+}}_{\substack{\text{stress fibre} \\ \text{disassembly}}}}$$

| | | | |
|---|---|---|---|
| $c_G$ | = G-actin concentration | $n_B$, $n_A$ | = barbed / pointed filament ends |
| $c_F$ | = F-actin concentration | $k_p^+$, $k_p^-$ | = polymerisation / depolymerisation rates |
| $c_{S+}$ | = mature stress fibre conc. | $k_m^-$ | = stress fibre disassembly rate |

# Key Constitutive Assumptions

## Adhesions drive stress fibre formation

### ROCK Activation Rate

$$k_R^+ = K_R^+ \times (n_B + \delta \times n_A)$$

$\delta = 4$ amplifies the contribution of mature focal adhesions ($n_A$) relative to nascent bound integrins ($n_B$).

Higher $\delta$ $\rightarrow$ stronger positive feedback $\rightarrow$ faster cytoskeletal assembly.

### Downstream effects of ROCK activation:

- Phosphorylates **cofilin** $\rightarrow$ reduces F-actin depolymerisation $\rightarrow$ more actin filaments
- Phosphorylates **MLCP** $\rightarrow$ reduces myosin II inactivation
- Phosphorylates **MLCK** $\rightarrow$ increases myosin II activation
- Net result: more stress fibres form and mature

## Stress fibres drive adhesion maturation

### FA Maturation Rate (Hill Function)

$$k_F^+ = K_F^+ \times g_s\left(\frac{c_{S^+}}{C_A}\right)$$

$$g_s = \frac{(c_{S^+}/C_A)^\alpha}{(c_{S^+}/C_A)^\alpha + \beta^\alpha}$$

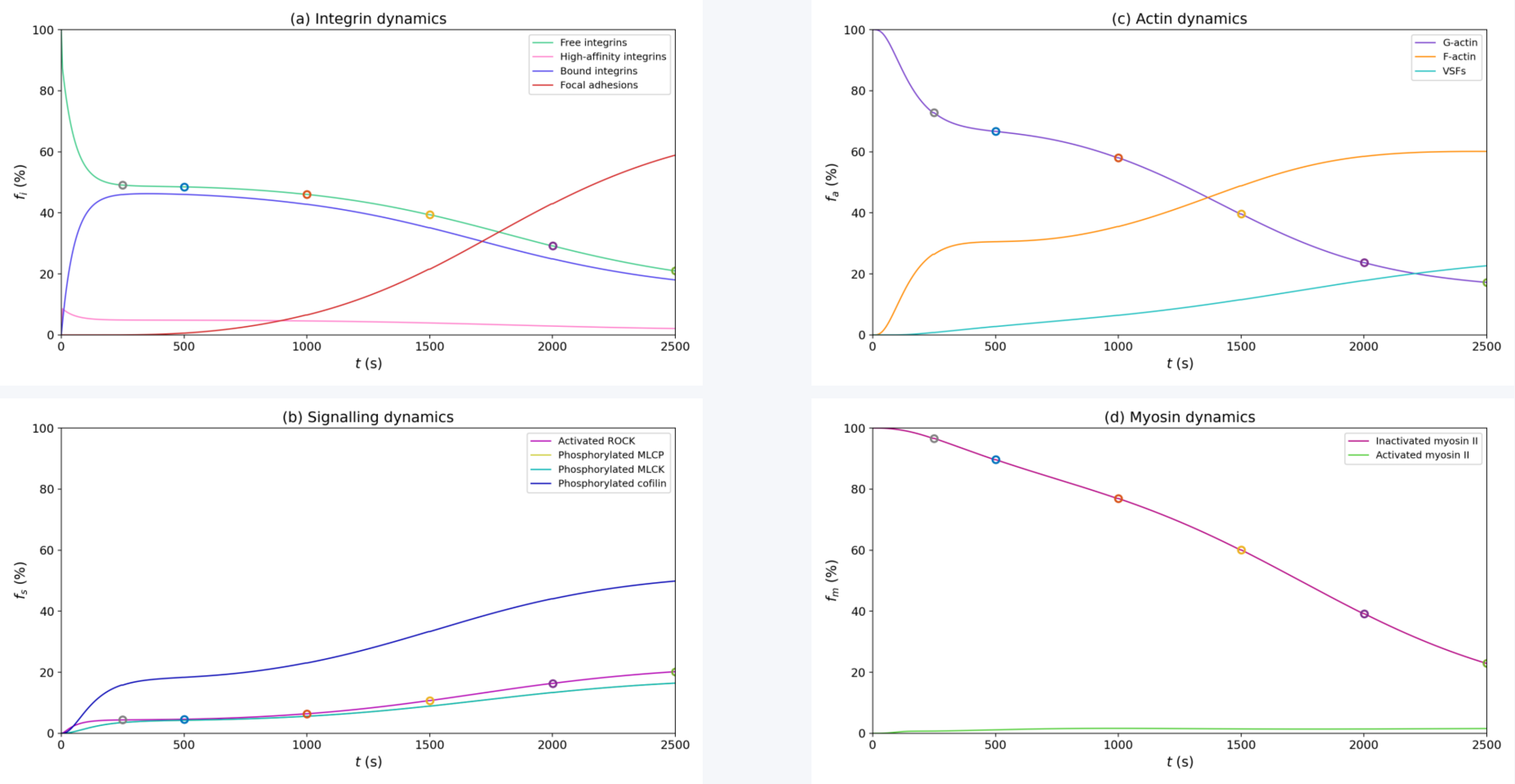
$\alpha = 2$ controls cooperativity (switch-like behaviour)

$\beta = 0.25$ sets the half-maximal VSF concentration

This creates a threshold: adhesions only mature once enough stress fibres have formed.

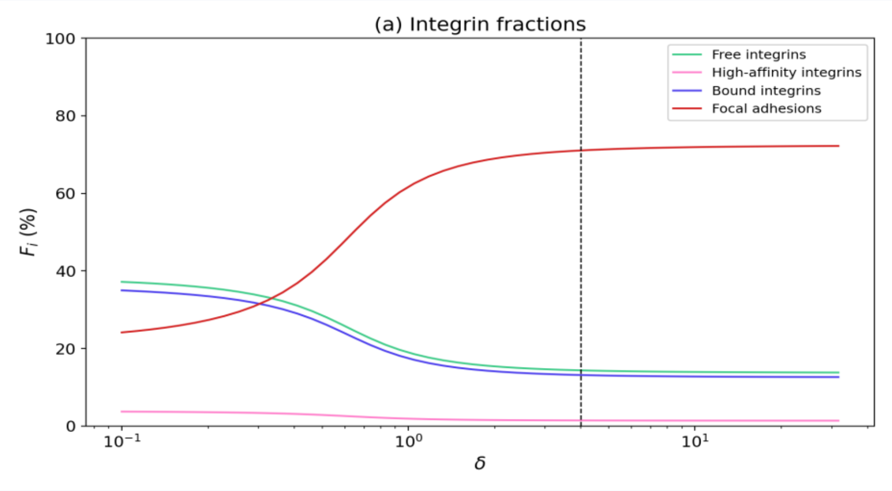
**We selected three parameters for sensitivity analysis: $\delta$ (feedback strength) · $n_{s_0}$ (substrate ligand density) · $k_{IR}^+$ (ROCK inhibitor binding rate)**

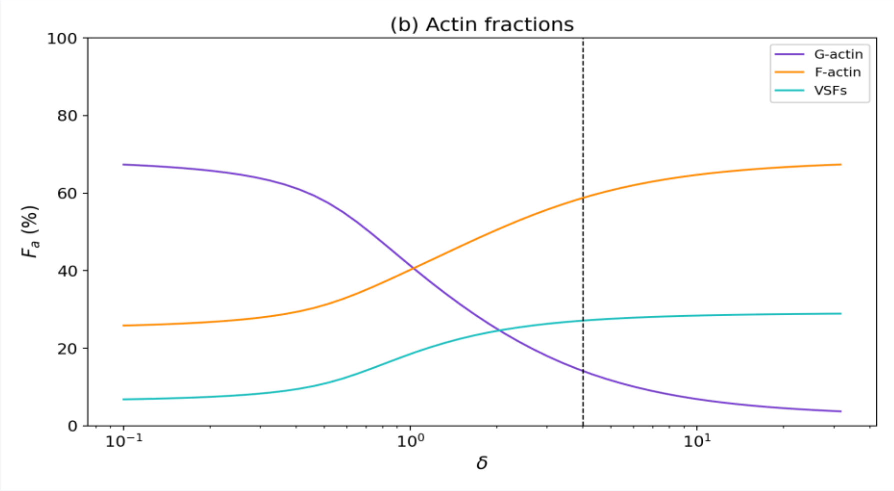
# Baseline: Adhesion & Cytoskeleton Assembly



# Sweep 1: δ — FA Feedback Strength

kR+ = KR+(nB + δ nA) | Sweep: δ ∈ [0.1, 31.6] | Baseline: δ = 4 (dashed line)



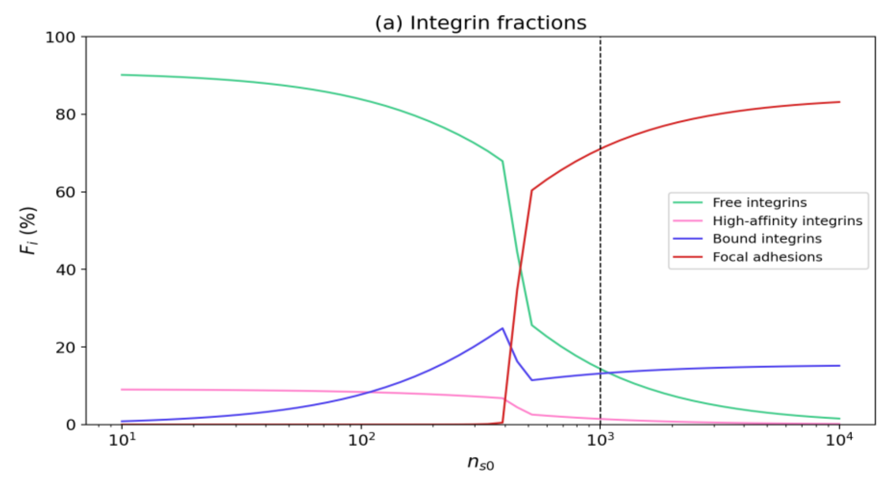

## δ — Internal feedback strength

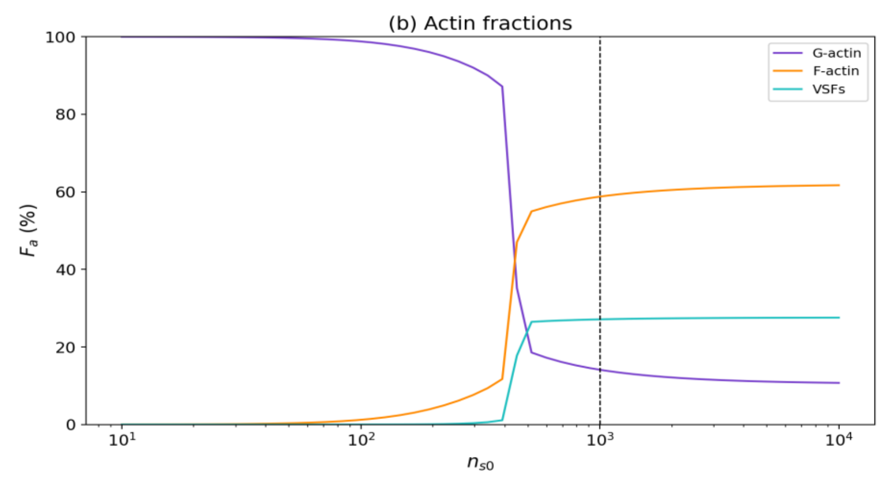
δ sits at the heart of the positive feedback loop. Changing it asks: how sensitive is the cell to its own signaling? Does the system need strong feedback to function, or is it robust?

*Understanding feedback robustness matters for diseases where signalling is dysregulated — e.g., fibrotic cells with high ROCK activity.*

# Sweep 2: ns0 — Substrate Ligand Density

ECM binding site density | Sweep: ns0 ∈ [10, 10000] | Baseline: ns0 = 1000 (dashed line)



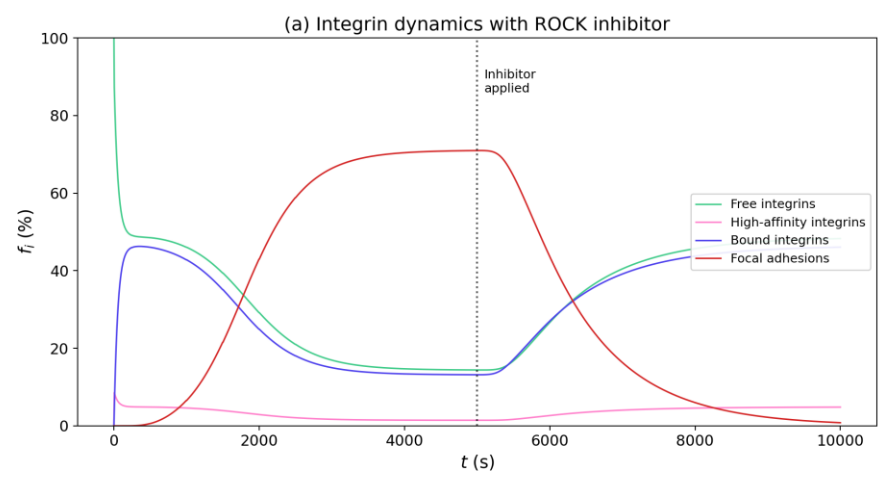



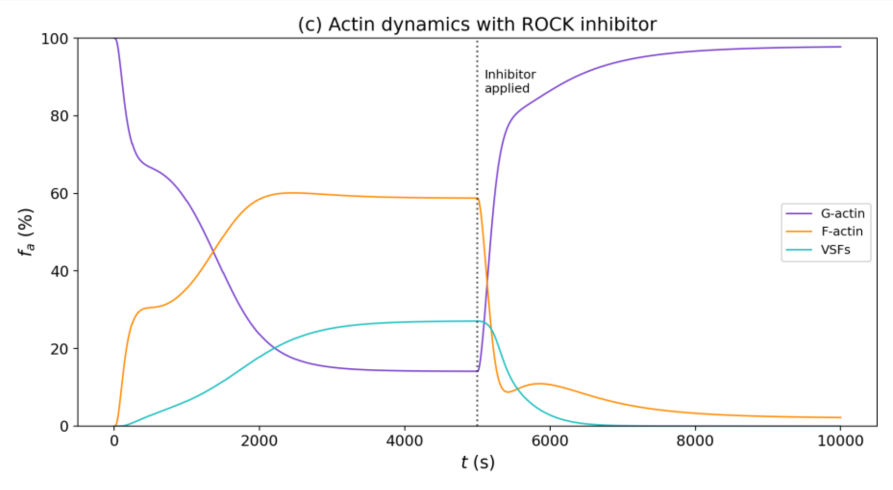

## ns0 — External environment (ECM density)

This is the upstream input the cell cannot control. Changing ns0 asks: what environmental conditions does the cell need to even begin mechanotransduction?

*Directly relevant to tissue engineering — if you're designing scaffolds, you need to know the minimum ligand density for cell adhesion.*

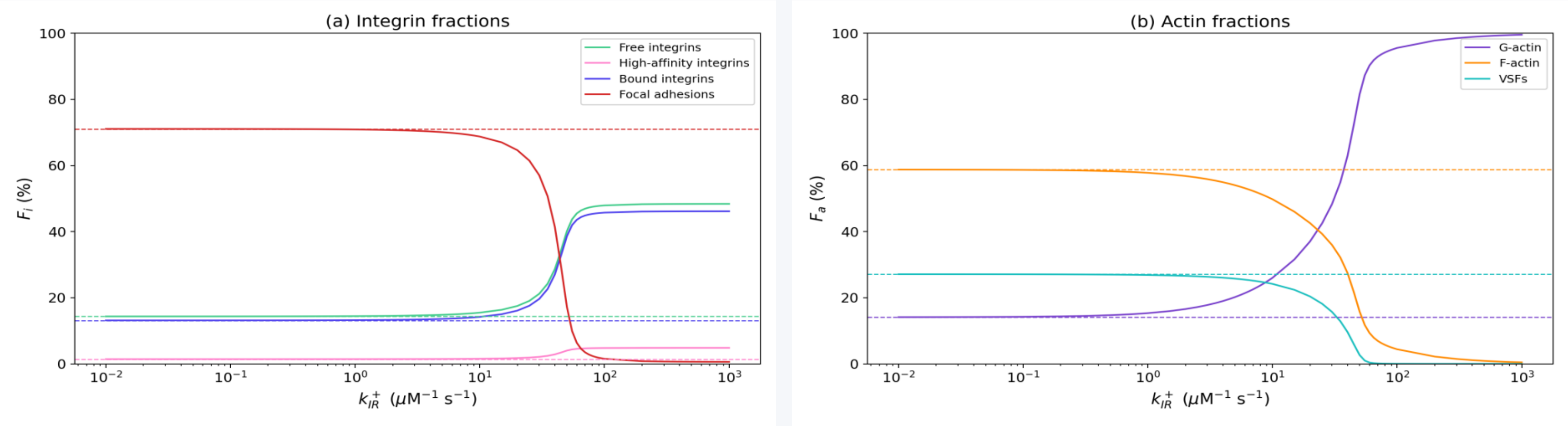
# ROCK Inhibitor: Time-Series Response



# Sweep 3: kIR+ — Inhibitor Dose-Response

Inhibitor–ROCK binding rate | Sweep: kIR+ ∈ [0.01, 1000] $\mu M^{-1}s^{-1}$ | Dashed = uninhibited baseline




## kIR+ — Pharmacological perturbation

ROCK inhibitors are real drugs used in research and clinical trials. This sweep asks: can we predict the dose-response curve from first principles?

Experimental titration data for ROCK inhibitors exists — our predictions could be directly compared and tested.

# Key Findings

1

## δ — Internal feedback architecture

Controls a positive feedback switch. The baseline δ = 4 sits in the saturated regime, meaning the cell is robust to small perturbations in feedback strength.

2

## ns0 — External mechanical environment

Acts as a gatekeeper. Below ~200 substrate sites, the entire mechanotransduction cascade is off. The steepest transition of all three sweeps, due to dual rescaling effects.

3

## kIR+ — Pharmacological intervention

ROCK inhibition reverses the adhered state dose-dependently. Integrins still bind but cannot mature — a specific prediction that could be tested microscopically.

✦

## Universal observation: Myosin II quasi-steady state

Activated myosin stays at ~2–3% across ALL sweeps. It is consumed by the fast cross-linking reaction as fast as it is produced — a transient intermediate, not a bottleneck.

# What This Tells Us

## Why it matters

- The model predicts that cells operate as bistable switches — they are either fully adhered or not at all. There is no halfway state. This has direct implications for understanding how cells commit to adhesion.
- The threshold behavior of ns0 explains why cells fail to spread on poorly coated substrates — not because spreading is gradual, but because the feedback loop simply cannot ignite below a critical ligand density.
- The inhibitor results predict a specific, testable signature: ROCK-inhibited cells should show increased nascent adhesions but no focal adhesions. This could be verified by immunofluorescence microscopy.

## Broader significance

### Tissue engineering

Knowing the ns0 threshold tells scaffold designers the minimum coating density required for cell adhesion — below this, no amount of signaling will help.

### Drug development

The kIR+ dose-response curve provides a quantitative framework for predicting ROCK inhibitor efficacy. The two-decade transition width suggests a narrow therapeutic window.

### Cancer biology

Tumour cells often show altered mechanosensing. This model framework could be extended to predict how mutations in ROCK or integrin pathways shift the adhesion switch point.

### Mathematical insight

The activated myosin quasi-steady state is a non-obvious prediction that emerges from the coupled dynamics — it shows why simple rate-limiting-step intuition can be misleading in feedback systems.

# Thank You

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*Questions?*