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Spatiotemporal model of cellular mechanotransduction via Rho and YAP

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Abstract

How cells sense and respond to mechanical stimuli remains an open question. Recent advances have identified the translocation of Yes-associated protein (YAP) between nucleus and cytoplasm as a central mechanism for sensing mechanical forces and regulating mechanotransduction. We formulate a spatiotemporal model of the mechanotransduction signalling pathway that includes coupling of YAP with the cell force-generation machinery through the Rho family of GTPases. Considering the active and inactive forms of a single Rho protein (GTP/GDP-bound) and of YAP (non-phosphorylated/phosphorylated), we study the cross-talk between cell polarization due to active Rho and YAP activation through its nuclear localization. For fixed mechanical stimuli, our model predicts stationary nuclear-to-cytoplasmic YAP ratios consistent with experimental data at varying adhesive cell area. We further predict damped and even sustained oscillations in the YAP nuclear-to-cytoplasmic ratio by accounting for recently reported positive and negative YAP-Rho feedback. Extending the framework to time-varying mechanical stimuli that simulate cyclic stretching and compression, we show that the YAP nuclear-to-cytoplasmic ratio’s time dependence follows that of the cyclic mechanical stimulus. The model presents one of the first frameworks for understanding spatiotemporal YAP mechanotransduction, providing several predictions of possible YAP localization dynamics, and suggesting new directions for experimental and theoretical studies.

Key words: YAP activation; Rho GTPase signalling; YAP nuclear translocation; cell polarization; mechanotransduction; protein oscillations

INSIGHT BOX

Our paper provides so far unprecedented insight into the dynamics of the Yes-associated protein (YAP). YAP has a pivotal role in regulating cell division and motility, and although its localization to the nucleus or the cytoplasm is crucial for performing that role, no detailed model of its spatiotemporal dynamics within cells exists to our knowledge. Our computational model gives detailed information about the distribution of YAP and predicts several regimes for its dynamics, including one characterized by sustained oscillations. As the relevant time scales have not yet been probed in the laboratory, our work suggests new directions for experimental research.
INTRODUCTION

In response to an external mechanical cue, cells balance their shape and cytoskeletal structure through internal forces, creating mechanical feedback. In multicellular tissues, intracellular forces are then transmitted to neighbouring cells through cell–cell junctions. Forces acting within cells provide them with a mechanism to maintain and alter their shape, but what instructs a cell to react in a specific way, e.g. divide, die or move, in response to different forces?

Inside a cell, a plethora of biochemical signalling pathways work together to induce a specific mechanical response [1, 2]. Therefore, to reveal the mechanical basis of mechanotransduction, it is beneficial to seek simple and flexible model systems.

In recent years, a single transcription factor, the Yes-associated protein (YAP) and its parologue TAZ [3], have been identified as the central hub for different signalling pathways and the master regulators of mechanotransduction [1, 3–10]. In response to different mechanical stimuli, such as tension or compression, YAP relocates between the cell nucleus and cytoplasm, regulating the cell response by switching between active (nuclear) and inactive (cytoplasmic) states [3]. As such YAP mechanotransduction controls a wide range of cell behaviours such as self-renewal, differentiation, proliferation, stemness, and apoptosis [1, 3, 7, 11]. At the multicellular level, this protein exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties: unrestrained proliferation-cell survival exerts control on organ size [3, 11] and is associated with most malignant properties.
Spatiotemporal model of cellular mechanotransduction via Rho and YAP

Figure 1. (A) Cartoon of our model for the mechanotransduction in the cell. GTP-bound activated Rho ($A_{act}$) localizes to the cell membrane and is both produced from and converted into its cytosolic inactive form ($A_{inact}$), which is bound to GDP. This generates a gradient in Rho that activates YAP and through stimulating the formation of actin cables (thick dashed lines) causes its active form ($Y_{act}$), which is produced from and degraded to phosphorylated inactive YAP ($Y_{inact}$, YAP-P), to localize to the nucleus. In turn, nuclear YAP affects the balance between active and inactive Rho. In addition to participating in chemical reactions, all species diffuse through the cell. (B) Schematic of our model for the mechanotransduction signalling pathway illustrating the various feedback mechanisms in the system. (C) Mapping of the model to 1D. (D) Harmonic potential acting on YAP in the nuclear region. (E) Diffusion coefficients for the two forms of YAP in our 1D representation of the cell. The active form (solid line) binds to TEAD in the nucleus, which corresponds to a drop in its diffusivity in that region, whereas the diffusion coefficient of the inactive form (dashed line) is uniform throughout the cell.

We base our expression for the rate of generation of active Rho on a well-known model according to which the concentration of the active form of Rho forms polarized stationary profiles (‘pinned waves’) [32]:

$$f_A(A_{act}, A_{inact}, Y_{act}) = c_1 + c_2 A_{act}^2 - c_4 A_{act} + c_5 \left( 1 - \frac{\int_{nucl} Y_{act} dS}{Y_{act, nucl, threshold}} \right),$$

where $c_1 - c_4$ are constants (see Table 1 for their units), $c_5$ is measured in s$^{-1}$C$_{DA}$, and the integral is over the extent of the nucleus $S_{nucl}$. The first two terms in equation (5), whose form we take from Ref. [32], allow for bistable behaviour of $A_{act}$ [32], for which there is experimental evidence [39]. With $c_5 = 0$ and suitable values for the other constants (see Table 1), a local perturbation to the homogeneous system can generate a concentration profile that takes approximately the value of one stable stationary solution for $A_{act}$ on one end of the cell, reaches the approximate value of the other stable stationary $A_{act}$ on the opposite end, and undergoes a steep transition in between.

Rate of Rho generation

$$\frac{\partial A_{act}}{\partial t} = \nabla \cdot (D_{A_{act}} \nabla A_{act}) + f_A(A_{act}, A_{inact}, Y_{act});$$

$$\frac{\partial A_{inact}}{\partial t} = \nabla \cdot (D_{A_{inact}} \nabla A_{inact}) - f_A(A_{act}, A_{inact}, Y_{act});$$

$$\frac{\partial Y_{act}}{\partial t} = -\nabla \cdot J_{Y_{act}} + f_Y(A_{act}, Y_{act}, Y_{inact});$$

$$\frac{\partial Y_{inact}}{\partial t} = -\nabla \cdot J_{Y_{inact}} - f_Y(A_{act}, Y_{act}, Y_{inact}),$$

where $A_i$ and $Y_i$ are the concentrations of the different forms of Rho and YAP and $D_A$ are the diffusion coefficients of active and inactive Rho; note that $D_{A_{inact}} \gg D_{A_{act}}$ because the active form is bound to the cell membrane. $f_i$ denotes the rate of generation of the active form of Rho or YAP, the fluxes of the different YAP species are $J_{Y_i}$, and $t$ is time. We nondimensionalize the concentrations of the different forms of Rho by an arbitrary value $C_{DA}$ so that they correspond to those reported by Mori et al. [32], for YAP, we normalize the total amount in the cell $N_{Y} = \int_V (Y_{act} + Y_{inact}) dV$ to unity, with $V$ being the cell volume. We present a schematic diagram of the model network in Figure 1.

The following system of reaction–diffusion equations:

$$\frac{\partial A_{act}}{\partial t} = \nabla \cdot (D_{A_{act}} \nabla A_{act}) + f_A(A_{act}, A_{inact}, Y_{act});$$

$$\frac{\partial A_{inact}}{\partial t} = \nabla \cdot (D_{A_{inact}} \nabla A_{inact}) - f_A(A_{act}, A_{inact}, Y_{act});$$

$$\frac{\partial Y_{act}}{\partial t} = -\nabla \cdot J_{Y_{act}} + f_Y(A_{act}, Y_{act}, Y_{inact});$$

$$\frac{\partial Y_{inact}}{\partial t} = -\nabla \cdot J_{Y_{inact}} - f_Y(A_{act}, Y_{act}, Y_{inact}),$$

where $c_1 - c_4$ are constants (see Table 1 for their units), $c_5$ is measured in s$^{-1}$C$_{DA}$, and the integral is over the extent of the nucleus $S_{nucl}$. The first two terms in equation (5), whose form we take from Ref. [32], allow for bistable behaviour of $A_{act}$ [32], for which there is experimental evidence [39]. With $c_5 = 0$ and suitable values for the other constants (see Table 1), a local perturbation to the homogeneous system can generate a concentration profile that takes approximately the value of one stable stationary solution for $A_{act}$ on one end of the cell, reaches the approximate value of the other stable stationary $A_{act}$ on the opposite end, and undergoes a steep transition in between.
Table 1. Key parameters based on other sources. Note, however, that we use values of the chemical rate constants $c_1, c_2,$ and $c_4$ that are higher than those of Mori et al. by an order of magnitude. We do so because it appears that the simulations in that paper were conducted with a diffusion coefficient for active Rho 10 times lower than the value given in the text; slower diffusion of active Rho translates into a more robust gradient in $A_{act}$. Increasing the rate constants by the same factor leads to approximately the same sharp ‘pinned wave’ concentration profile as the one in Mori et al.’s Fig. 2a [32].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Meaning</th>
<th>Value</th>
<th>Units</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{A_{act}}$</td>
<td>Diffusion coefficient of active Rho</td>
<td>$10^{-13}$</td>
<td>$m^2 \cdot s^{-1}$</td>
<td>[56]</td>
</tr>
<tr>
<td>$D_{A_{inact}}$</td>
<td>Diffusion coefficient of inactive Rho</td>
<td>$10^{-11}$</td>
<td>$m^2 \cdot s^{-1}$</td>
<td>[56]</td>
</tr>
<tr>
<td>$D_{Y_{cyto}}$</td>
<td>Diffusion coefficient of YAP in the cytoplasm</td>
<td>$8 \times 10^{-11}$</td>
<td>$m^2 \cdot s^{-1}$</td>
<td>[54]</td>
</tr>
<tr>
<td>$D_{Y_{nucl}}$</td>
<td>Diffusion coefficient of YAP in the nucleus</td>
<td>$4.5 \times 10^{-12}$</td>
<td>$m^2 \cdot s^{-1}$</td>
<td>[54]</td>
</tr>
<tr>
<td>$L$</td>
<td>Cell length</td>
<td>$10^{-5}$</td>
<td>$m$</td>
<td>[32]</td>
</tr>
<tr>
<td>$c_1$</td>
<td>Base activation rate for Rho</td>
<td>$0.67$</td>
<td>$s^{-1}$</td>
<td>[32]</td>
</tr>
<tr>
<td>$c_2$</td>
<td>Hill function parameter for Rho</td>
<td>$10$</td>
<td>$s^{-1}C_{0A}^{-2}$</td>
<td>[32]</td>
</tr>
<tr>
<td>$c_3$</td>
<td>Hill function parameter for Rho</td>
<td>$10$</td>
<td>$C_{0A}$</td>
<td>[32]</td>
</tr>
<tr>
<td>$c_4$</td>
<td>Base deactivation rate for Rho</td>
<td>$10$</td>
<td>$s^{-1}$</td>
<td>[32]</td>
</tr>
</tbody>
</table>

(‘pinned wave’). This concentration profile is a 1D representation of a polarized cell state.

We introduce the last term in equation (5) to account for the coupling between Rho and nuclear YAP. This is motivated by recent experiments that demonstrate the existence of both positive feedback of nuclear YAP on Rho via ARHGAP 28 and negative feedback via ARHGAP 29 and NUAK2 [40]. However, neither the relative magnitudes of these feedbacks are known, nor whether or under what conditions the overall effect of YAP on Rho can assume that activation of Rho generates tension that stretches the cell nucleus and drives the nuclear localization of active YAP. Such forces are known to originate from perinuclear stress fibres [43], and stress fibre formation is thought to be controlled by Rho [42]. Our assumption of YAP-specific nuclear transport is supported by experimental data from Kofler et al. [35]. Their observations of nuclear transport specific to TAZ led them to hypothesize that force-induced changes in the nuclear pore complex may ‘stimulate sequence-specific, mediated import of TAZ’ [35].

We therefore relate the force active YAP is experiencing, $F$, to its flux towards the nucleus,

$$J_{act}^{nuclear tension} = Y_{act} F_{act} - Y_{act} F_{act},$$

where we assume overdamped dynamics, which means that the velocity $v_{act}$ is simply related to $F$ through the friction coefficient $\xi$. $F$ is an effective measure of the amount of nuclear tension and thus implicitly accounts for cell deformation, stretching, and compression. Since the magnitude of the mechanical stress $|\sigma|$ associated with the tension is normally expressed to be proportional to the concentration of actomyosin that is controlled by the active form of Rho, $|\sigma| \sim A_{act}$ [44–50], we expect the force to be proportional to the gradient of active Rho.

We assume that the tension in the stress fibres is controlled by the value of this gradient averaged over the whole cell and obtain the expression $|\sigma| = \langle |\nabla A_{act}| \rangle$, with spatially averaged defined via $(X) = \int_{S_{cell}} X dS / S_{cell}$; depending on the dimensionality of the model, $S_{cell}$ is the length, area, or volume of the cell. This form of $|\sigma|$ is consistent with the accepted paradigm that as the cell polarizes and the gradients in Rho are established, tension is enhanced within the actin cable, leading to cell stretching and spreading on the substrate [47–50]; note that here we assume linear proportionality between the concentrations of active Rho and actin.

**Flux of active YAP**

Next, we describe the spatiotemporal evolution of YAP that is controlled through two Rho-dependent pathways: nuclear localization driven by the actin cytoskeleton and myosin-contraction-regulated inactivation through phosphorylation (see e.g. [38]). Both pathways are effectively controlled by Rho, which regulates the polymerization of actin via mDia and myosin activity via Rho-associated protein kinase (ROCK) [26, 29, 42].

First, we consider the flux of active YAP to the nucleus $J_{Y_{act}}^{nuclear tension}$ due to the mechanical tension generated by the cytoskeleton. Based on recent experimental data that suggest deformation of the nucleus is key to activating YAP [8, 22, 43], we assume that activation of Rho generates tension that stretches the cell nucleus and drives the nuclear localization of active YAP. Such forces are known to originate from perinuclear stress fibres [43], and stress fibre formation is thought to be controlled by Rho [42]. Our assumption of YAP-specific nuclear transport is supported by experimental data from Kofler et al. [35]. Their observations of nuclear transport specific to TAZ led them to hypothesize that force-induced changes in the nuclear pore complex may ‘stimulate sequence-specific, mediated import of TAZ’ [35].

We therefore relate the force active YAP is experiencing, $F$, to its flux towards the nucleus,
following the analogy, we can think of $q = \xi^{-1}$ as an effective charge; if all quantities were dimensional, $q$ would have units of $m^2 s^{-1} C_2^2$.

For simplicity, here we consider the cell as a one-dimensional system and use a harmonic potential $\phi$ whose gradient is

$$d\phi = \begin{cases} x_n\text{nucl front} - x_n\text{nucl back} & \text{if } t > 0 \text{ and } x_n\text{nucl front} \leq x \leq x_n\text{nucl back} \\ 0 & \text{otherwise}. \end{cases}$$

$x$ is a spatial coordinate nondimensionalized by the cell length, $L = 1 \times 10^{-5}$ m; $x_n\text{nucl}$ i are the coordinates of the front and the back of the nucleus; here, we fix them to $x_n\text{nucl front} = 1/3$ and $x_n\text{nucl back} = 2/3$. With this choice of $\phi$, its gradient is nondimensional and has a maximum absolute value that is normalized to unity.

**Flux of active YAP in the absence of a stimulus.** Experimental data indicate that when cells are subjected to conditions that do not stimulate division and motility, i.e. when their adhesive area is low and/or they are seeded on a soft substrate, they exhibit a ratio of nuclear to cytoplasmic YAP, $R = \int_{x_n\text{cyt}} Y_{\text{act}} + Y_{\text{inact}} dx / \int_{x_n\text{cyt}} Y_{\text{act}} + Y_{\text{inact}} dx$, approximately equal to 1, see e.g. [22, 38, 52]. Inactive YAP is sequestered to the cytoplasm where it binds to the protein 14-3-3 [37, 53], which means that if the nucleus is smaller in volume than the cytosol, the nuclear-to-cytoplasmic YAP ratio can only be $\approx 1$ if active YAP is attracted to the nucleus even in the absence of Rho activation. This suggests an additional term in the flux of $Y_{\text{active}}$,

$$J_{Y_{\text{act}}}^\text{rest} = -q_0 Y_{\text{act}} \nabla \phi,$$

where the effective charge in the absence of stimulation ($q_0$) would be measured in units of $m s^{-1}$ if all quantities were dimensional.

The total flux of active YAP is the sum of the contributions in equations (6) and (8) and the diffusional flux of the species,

$$J_{Y_{\text{act}}} = J_{Y_{\text{act}}}^\text{nuclear tension} + J_{Y_{\text{act}}}^\text{rest} - D_{Y_{\text{act}}} V Y_{\text{inact}} = -(q_0 + q (\nabla A_{\text{act}})) Y_{\text{act}} \nabla \phi - D_{Y_{\text{act}}} V Y_{\text{act}}.$$

**Flux of inactive YAP**

Similarly, the flux of inactive YAP contains a diffusional contribution and one due to its sequestering by 14-3-3, which we model via a term that repels it from the nucleus. Since YAP phosphorylated at serine 112 forms a complex with 14-3-3 [38], we assume that this interaction is unaffected by mechanical stimuli and introduce a term that repels inactive YAP from the nucleus regardless of the polarization of the cell with respect to active Rho,

$$J_{Y_{\text{inact}}} = q_1 Y_{\text{inact}} \nabla \phi - D_{Y_{\text{inact}}} V Y_{\text{inact}}$$

where the effective charge for inactive YAP ($q_1$) has units of $m s^{-1}$.

Since activated YAP is transferred to the nucleus, where it binds to the transcription factor TEAD [8], its diffusion in this region is impaired. An approximate way of taking that into account is to assume that $D_{Y_{\text{inact}}}$ varies smoothly from its cytoplasmic value to that for the nuclear region, and in particular that its profile is given a hyperbolic tangent (see the Supporting Information for the precise form we use). Note that this assumption likely overestimates the effect of YAP–TEAD binding as the 1D model only allows diffusion through the nucleus but not around it. For the same reason, we fix the diffusion coefficient of the inactive form of YAP to the value measured for it in the cytoplasm as an average for the two species, $DY_{\text{inact}}$ [54].

**Rate of YAP generation**

Finally, the rate of generation of active YAP, $f_Y$, includes two contributions—one due to first-order self-activation, which is proportional to the concentration of inactive YAP, and one due to deactivation via, e.g. the LATS pathway, see [5, 53, 55]. Experimental data indicate that inhibiting myosin contractility either directly with blebbistatin or via inhibiting ROCK with Y-27632 causes an increase in the relative abundance of the inactive form of YAP that is phosphorylated at serine 112 [38]. For this reason, we introduce a term in the rate of interconversion between active and inactive YAP that favours the active form at high myosin contractilities, and vice versa. Myosin is indirectly activated by Rho, and by the same argument we applied to modelling Rho-induced nuclear tension, we assume that myosin contractility is proportional to the average gradient in active Rho. Furthermore, we assume that the myosin-regulated YAP activation saturates, which we model with a first-order Hill function. Combining both contributions, we arrive at the following expression for the rate of chemical generation of active YAP:

$$f_Y (A_{\text{act}}, Y_{\text{act}}, Y_{\text{inact}}) = c_0 Y_{\text{inact}} - c_7 Y_{\text{act}} \left( 1 - \frac{c_6 (\nabla A_{\text{act}})}{c_0 + c_6 (\nabla A_{\text{act}})} \right);$$

(11)

to keep the units consistent, $c_6$ and $c_7$ are measured in $s^{-1}$, $c_8$ and $c_9$ are measured in $C_2^{-1} L$, and $c_4$ is dimensionless. The values of the parameters for the rate of YAP generation are listed in Table A.1 in the Supporting Information.

It is worthy of note that due to the presence of the average active Rho gradient in equations (9) and (11), as well as that of the amount of active YAP in the nucleus in equation (5), our reaction–diffusion equations (1)–(4) are partial integro-differential rather than simply differential equations; moreover, they are non-linear.

**METHODS**

We solve equations (1)–(4) by performing updates of the integral terms at discrete intervals $\Delta t$ and treating them as constant within each such interval. This allows us to use the 1D partial differential equation solver built into MATLAB R2020a (9.8.0.1451342), pdepe, which employs a second-order finite-element discretization in space and a variable-step, variable-order algorithm for time integration (ode15s), see Ref. [57]; pdepe ensures flux continuity in the solution region [58]. We use a uniform grid of 250 mesh points for spatial discretization and set $\Delta t$ such that it is considerably smaller than the time scale for the fastest process that occurs in a system with a particular set of parameters; $\Delta t$ thus varies in the range $1 \times 10^{-4} s - 1 \times 10^{-1} s$. We assume that the total amounts of YAP and Rho in the cell are conserved and therefore impose no-flux boundary conditions at both ends of the cell for all species,

$$n \cdot \nabla Y_{\text{act}}|_{x=\pm L} = n \cdot \nabla A_{\text{act}}|_{x=0} = 0,$$  

(12)

where $n$ is the outward normal to the cell boundaries.
Equilibration and initial perturbations

We investigate the dynamics of YAP localization upon the introduction of a perturbation in the concentration of active Rho. To do this, we first let the system equilibrate in the absence of any stimuli. We use homogeneous initial conditions for the GTPase: $A_{\text{inact}} = 20$ and $A_{\text{act}} = A_{\text{act}}^0 = 2.683$, $A_{\text{act}}^0$ being the lower stable steady concentration that corresponds to this value of $A_{\text{inact}}$, obtained as a solution to the equation $f_A(A_{\text{act}}, A_{\text{inact}}, Y_{\text{act}})|_{t=0,t}$. The simulation starts with a homogeneous YAP distribution that includes no active form, $Y_{\text{act}} = 0$ and $Y_{\text{inact}} = 1$.

Due to the terms proportional to $q_0$ and $q_1$, the YAP concentrations evolve so that the active form has a peak in the nucleus and the inactive form is depleted from it. The concentration profiles of the two forms of Rho remain homogeneous but change because, due to the $c_5$ term, $A_{\text{act}}$ is no longer a stationary concentration. All concentration distributions reach a steady state within $\sim 10$ s.

We simulate the equilibration of the system for each set of kinetic parameters (see Figure A.1(c) in the Supporting Information). We then apply a localized parabolic initial perturbation to the stationary Rho concentration profiles obtained from this simulation, $A_{\text{stat}}$. The form of the perturbation preserves the overall amount of Rho GTPase in the system and obeys no-flux boundary conditions,

$$
\delta A_{\text{act}} = A_{\text{pert}} A_{\text{act}} \text{stat} \left(1 - \frac{x}{L_{\text{pert}}}^2\right) \text{Heaviside} \left(L_{\text{pert}} - x\right) \quad (13)
$$

with

$$
A_{\text{act}}|_{t=0} = A_{\text{act}} \text{stat} + \delta A_{\text{act}} \quad (14)
$$

and

$$
A_{\text{inact}}|_{t=0} = A_{\text{inact}} \text{stat} - \delta A_{\text{act}}. \quad (15)
$$

Unless otherwise noted, we use $A_{\text{pert}} = 0.75$ and $L_{\text{pert}} = 0.15$; the effect of varying $A_{\text{pert}}$ is shown in Figure A.2 in the Supporting Information. In most simulations, localized perturbations of this form with a sufficiently large amplitude generate a polarized profile of $A_{\text{act}}$ with a region of high concentration $A_{\text{act}}$ in the vicinity of the initial stimulus, a region of low $A_{\text{act}}$ on the other end of the cell, and a steep gradient in between (‘pinned wave’). This happens because, as per equation (5), the production of active Rho is an autocatalytic reaction, and a local increase of $A_{\text{act}}$ sufficiently large not to be dispersed by diffusion leads to its accumulation. At the same time, the positive feedback of $A_{\text{act}}$ on itself is limited because of the second-order Hill function in equation (5), which leads to a plateau in $A_{\text{act}}$. This simulates the behaviour of a cell, which receives an external stimulus and acquires polarization due to spatial variations in the concentration of GTP-bound Rho.

We examine the effect of the form of the initial conditions on the system’s dynamics by using an alternative way of inducing a gradient in Rho, following Mori et al. [32]. At short times, we add a transient local stimulus term of the form $k_{\text{stim}} A_{\text{inact}}$ to $f_A(A_{\text{act}}, A_{\text{inact}}, Y_{\text{act}})$

$$
k_{\text{stim}} = s(t) \left(1 + \cos(\pi x)\right) \text{Heaviside} \left(L/10 - x\right), \quad (16)
$$

where

$$
s(t) = 
\begin{cases} 
\frac{S_{\text{Ampl}}}{2} & \text{if } 0 \leq t \leq t_1; \\
\frac{S_{\text{Ampl}}}{4} \left[1 + \cos \left(\frac{\pi}{t_1 - t_2} \left(t - t_2\right)\right)\right] & \text{if } t_1 \leq t \leq t_2; \\
0 & \text{otherwise},
\end{cases}
$$

with $S_{\text{Ampl}} = 0.5$, $t_1 = 20$ and $t_2 = 25$ [32]; as with $c_1$, $c_2$ and $c_4$, we increase the value of $S_{\text{Ampl}}$ tenfold from the one reported in the paper to compensate for the mistake in the diffusion coefficient of active Rho in Ref. [32]. The two types of initial conditions—equations (13)–(15) versus equations (16)–(17) are compared in Figure A.2 in the Supporting Information.

**RESULTS**

Here we discuss the specific predictions of the model for different parametrizations of the coupling between YAP and Rho: (1) non-oscillatory and (2) oscillatory YAP/Rho dynamics at mechanical stimuli ($q$) of fixed magnitude; (3) YAP/Rho dynamics for time-dependent $q$.

Non-oscillatory YAP/Rho dynamics at a fixed mechanical stimulus magnitude ($q$)

Experimental studies show that the ratio of nuclear to cytoplasmic YAP ($R$) is close to unity for unstimulated cells and can increase up to severalfold upon the application of a mechanical stimulus that most typically increases the cell’s adhesive area—see e.g. Ref. [52], where the ratio varies from $\approx 1$ to $\approx 3$, and Ref. [59], where it saturates at $\approx 5$.

With this in mind, we choose parameters for our simulations that yield a YAP ratio of $\approx 1$ when the Rho concentration profile in the cell is not polarized: $c_5 = 1$, $c_6 = 1$, $c_7 = 1$, $c_8 = 3.5$, $c_9 = 1$, $c_{10} = 5$, $q_0 = 2.5$, $q_1 = 2$, see the red line in Figure 2. We begin by considering strictly positive feedback of YAP on Rho, $Y_{\text{act}}$ nucleus threshold $= 1$. Upon the application of a sufficiently strong perturbation, the system forms a stationary polarized state and the gradient in Rho increases the amount of active YAP in the nucleus both by directly increasing the effective depth of the potential well (eq. (6)) and by favouring the formation of the active form through the Hill-function term in equation (11).

We perform a set of simulations in which we vary the value of $q$, and in this way explore the dynamics of YAP and Rho relaxation upon application of a constant mechanical stimulus. We then calculate the stationary nuclear-to-cytoplasmic YAP ratios $R$ at $t = 250$ s, when the system has reached a steady state (see Figure 2). As the figure indicates, $R$ increases steeply in the range $q \sim 10^{-2} - 1$ and plateaus at higher $q$. Moreover, the stationary YAP ratios are the same regardless of whether we employ a parabolic initial perturbation in concentration (blue circles) or a transient initial stimulus (red crosses), although the system takes a different path to the stationary state.

Oscillations in YAP and Rho activity at fixed $q$

Next, we study the nuclear-to-cytoplasmic YAP ratio for systems with both positive and negative feedback of YAP on Rho. This is motivated by recent experiments that demonstrated the possibility for feedback of either sign mediated by ARHGAP proteins [40]. Interestingly, in the presence of both types of feedback, the system shows both damped and sustained oscillations of the YAP nuclear-to-cytoplasmic ratio for a range of
Figure 2. (a) Stationary nuclear-to-cytoplasmic YAP ratios ($R$) for simulations at different intensities of the mechanical stimulus $q$. The red line gives $R$ for the case with no stimulus in which the concentration profiles of both forms of Rho remain homogeneous; the blue circles are obtained through simulations with a parabolic initial perturbation; the red crosses represent the YAP ratios in simulations with a transient initial stimulus as per equations (16)–(17). The YAP-Rho coupling for all these data points is weak and the parameters are: $c_5 = 1$, $c_6 = 1$, $c_7 = 1$, $c_8 = 5$, $c_9 = 1$, $c_{10} = 5$, $q_0 = 2.5$, $q_1 = 2$, $Y_{act\ nucl\ threshold} = 1$. The asterisks represent simulations in which the final concentration profile exhibits a nonphysical second region of high $A_{act}$ in the nucleus; the triangles—to cells polarized as in the plot for $t = 50$ s in (b); squares—to simulations in which $R(t)$ oscillates in response to sufficiently large perturbations to $A_{act}$ (see Section 4.3 below), with error bars indicating the minimum and maximum value $R$ attains in the regime with sustained oscillations, and the pluses stand for simulations that yield damped oscillations in $R(t)$. The parameters for all these data points in black are: $c_5 = 30$, $c_6 = 1$, $c_7 = 1$, $c_8 = 2.5$, $c_9 = 1$, $c_{10} = 5$, $q_0 = 1.25$, $q_1 = 0.5$, $Y_{act\ nucl\ threshold} = 0.4$. (b) Snapshots of the evolution of the concentrations of the different species in the system at a low value of the mechanical forcing term $q$ and a weak YAP-Rho coupling. Rho (top row) and YAP (bottom row) profiles, with solid lines depicting active forms and dashed lines—inactive forms. The vertical lines indicate the boundaries of the nucleus. As seen in the plot for $t = 0$ s, the initial perturbation to the homogeneous Rho concentrations is parabolic.
the force magnitude $q$ and the strength of coupling between YAP and Rho. Oscillations can arise in our model as follows: for $Y_{\text{act nucl}} < 1$, feedback of nuclear YAP on Rho changes sign if $Y_{\text{act nucl}} > Y_{\text{act nucl threshold}}$. This reduces the gradient in active Rho, causing $Y_{\text{act nucl}}$ and the nuclear-to-cytoplasmic ratio $R$ to go down because of the weaker driving force for YAP nuclear translocation (eq. (5)) and YAP activation (eq. (11)). For suitable parameter values, polarization is not fully lost in this process $((\nabla Y_{\text{act}}) \neq 0)$ such that once $Y_{\text{act nucl}} < Y_{\text{act nucl threshold}}$ YAP activates Rho again, causing the gradient in active Rho to increase and $R$ to follow suit until $Y_{\text{act nucl}}$ reaches $Y_{\text{act nucl threshold}}$ and the cycle is reset. We illustrate this process through snapshots of the concentration profiles for two simulations in Figure 3: one of these (for $q = 0.48$) results in sustained oscillations, whereas the other (for $q = 0.96$) yields damped oscillations.

Apart from $Y_{\text{act nucl threshold}}$, the system’s behaviour is sensitive to the coupling constants that govern the effect of YAP on Rho ($c_3$) and that of Rho on YAP ($q$). We have found oscillations for $c_3 = 30$, a value much greater than the simulations in Figure 2 that exhibit non-oscillatory dynamics at $c_3 = 1$. For oscillations to occur, $c_3$ needs to be high enough that $\nabla q_{\text{act}}$ is significantly perturbed, but not so large that nuclear active YAP levels above $Y_{\text{act nucl threshold}}$ cause active Rho to adopt a uniform profile.

Moreover, the stationary $R$ tends to reach saturation with $q$ (see Figure 2(a)), which means that at high $q$, changes in the term $q(\nabla Y_{\text{act}})$ in the flux of nuclear YAP, equation (6), that fully preserve polarization and, as such, weakly affect $\nabla q_{\text{act}}$, will be too weak to cause a significant change in $R$. At the same time, if $q \rightarrow 0$, changes in $\nabla q_{\text{act}}$ will be too weak to affect $R$. The oscillatory regime thus requires $q$ to be in the range that roughly corresponds to the region of the curve in Figure 2(a) with the greatest slope. This is indeed what we see when we perform simulations at different $q$ and fixed other parameters: at $q \rightarrow 0$, $R$ reaches a stationary value without oscillating (notably, the profile of Rho develops a second region of high Rho activity), and at $q > 10$ the stationary state is reached within ~10 s after several damped oscillations. In the intermediate range, $q \sim 1$, illustrated in Figure 3, we see slowly damped oscillations at $q = 0.96$ and sustained ones at $q = 0.48$, both types with a period of ~1 s.

A pertinent question is whether these oscillations are robust with respect to changing the initial conditions. We tested this by conducting runs for different values of $A_{\text{pert}}$ in equation (13) and using the transient stimuli introduced by Morì et al. [32], equations (14)–(15). These tests, which are illustrated in Figure A.2 in the Supporting Information, show that perturbations that are too weak ($A_{\text{pert}} \lesssim 0.1$ at $q = 0.48$ and $A_{\text{pert}} \lesssim 10^{-2}$ at $q = 0.96$) do not excite oscillations in $R$. This happens because such perturbations are dispersed by diffusion and do not generate a polarized profile in active Rho; consequently, the concentrations of all species return to the equilibrium values calculated as per Section Equilibration and initial perturbations in this paper. However, if the initial perturbation is strong enough, it generates a pinned wave in $A_{\text{act}}$, which through its corresponding non-zero $\nabla A_{\text{act}}$ activates YAP. When the level of active nuclear YAP exceeds the threshold value, the system enters an oscillatory state like the ones illustrated in Figure 3. The comparison between $R(t)$ curves for different initial conditions in Figure A.2 (Supporting Information) shows that the frequency of the oscillations is unaffected by changes in $A_{\text{pert}}$, and that for the sustained case, the same is true of the amplitude after the initial transient. This is to be expected as due to the form of equation (5), the two attractors in this system are the equilibrated state with homogeneous Rho concentrations and the state with polarized Rho and $Y_{\text{act nucl}} = Y_{\text{act nucl threshold}}$.

The oscillations we describe here occur about the value of $R$ at which $Y_{\text{act nucl}} = Y_{\text{act nucl threshold}}$; thus, we can tune the stationary $R$ by changing $Y_{\text{act nucl threshold}}$. We illustrate this in Figure A.3 in the Supporting Information, where we change $Y_{\text{act nucl threshold}}$ from 0.4 to 0.425 in comparison with Figure 3b and see that in this case, $R(t)$ oscillates about $\sim 1.5$ rather than 1.15.

It is instructive to note that while transient YAP dynamics have been only marginally explored, oscillations in Rho have been reported in several experimental and theoretical studies. Miller and Bement [60] observed oscillations in Rho activity on a time scale of ~20 s during cytokinesis in cells in which the GTase activating protein MgcRacGAP is inactive. They hypothesized that although GAPs typically deactivate Rho proteins, MgcRacGAP in particular also anchors Rho-GTP and thus prevents oscillations from arising. Rho GTase (RhoA, CDC42, RAC1) activity has also been reported to correlate with cell protrusion formation, and to oscillate on a similar time scale during protrusion-retraction cycles [61]. Nikonova et al. [62] formulated an ODE-based model in which Rho activity is controlled by GDP dissociation inhibitors and can exhibit sustained oscillations with a period of ~10 s.

More recently, Franklin et al. [63] have looked into the dynamic evolution of the YAP nuclear-to-cytoplasmic ratio $R$ and observed large fluctuations on a time scale of hours during monolayer growth. Moreover, sustained oscillations in calcium levels induced via treatment with the drug Thapsigargin correlate with oscillations in nuclear area as well as low-amplitude oscillations in $R$, and the period for all three is of the order of 30 minutes. Additionally, there is indirect evidence that YAP activity may also oscillate in certain contexts. Dequèant et al. [64] reported that Cyr61, a key direct transcriptional target for YAP [65], is a cyclic gene of the mouse segmentation clock, leading Hubaud et al. [66] to hypothesize that the YAP pathway could be regulated in a periodic fashion. Cyr61 oscillations have a typical time scale of the order of hours [67], and one would expect a similar oscillation period for YAP activity if it is the source of these oscillations.

YAP/Rho dynamics for time-dependent $q$

Many experimental studies have looked at the effect of cyclic stretching and compression on tissues since such stimuli have relevance, for example, to the study of vascular cells as pulsatile pressure changes in blood pressure lead to expansion and compression of large arteries [68]. Recently, Landau et al. [69] have shown that applying cyclic stretching in a culture of endothelial cells and fibroblasts over multiple days leads to translocation of YAP to the nucleus in the fibroblasts and to the alignment of the latter perpendicularly to the direction of stretching. However, we are not aware of any studies that have characterized the effect on YAP activation on the time scale of the applied stretching.

Since our model couples biochemical signalling to mechanics via the effective charge $q$, we can study the effect of time-dependent mechanical stimuli on YAP and Rho activity. In particular, Figure 4 illustrates $R(t)$ for simulations with oscillatory $q(t)$ of the form

$$q(t) = q_{\text{initial}} \left(1 + \sin(2\pi vt)\right) \quad \text{(18)}$$

at frequencies $v$ ranging from $10^{-3}$ to 1 Hz; the other parameters are the same as in Figure 2, i.e. they yield $R$ in the same range as experimental data and do not allow for oscillations at a static $q$.

The nuclear-to-cytoplasmic YAP ratios for time-dependent $q$ in Figure 4 closely follow the external oscillations. This implies
Figure 3. Results from simulations with strong feedback of YAP on Rho ($c_5 = 30$) that switches sign at $Y_{\text{act nucl threshold}} = 0.4$. (a) Nuclear-to-cytoplasmic YAP ratios for $q = 0.48$ (solid line) and $q = 0.96$ (dotted line). Note that the lower $q$ value leads to sustained oscillations in the ratio, whereas the higher one—to damped oscillations. (b-c) As in the rest of the text, Rho profiles are in the top row and YAP profiles—in the bottom one, with solid lines depicting acting forms and dashed lines—inactive forms. The vertical lines indicate the boundaries of the nucleus. (b-c) Snapshots of the concentration distributions for the simulation at $q = 0.48$ (b) and $q = 0.96$ (c) illustrated in (a), taken at some of the peaks in $R$. The damping of $R$ in (c) comes from the damping in $\langle \nabla A_{\text{act}} \rangle$ (controlled by the values of $A_{\text{act}}$ at the endpoints, as indicated by the arrows in the plot), which is in turn caused by the stronger feedback between YAP and Rho at higher $q$, see equation (6). Red circles mark the points in time at which the concentration profile snapshots are taken.

that our proposed mechanism for YAP activation via Rho-induced nuclear tension could be behind the activation observed in systems subjected to cyclic stretching and compression.

DISCUSSION AND CONCLUSIONS

To our knowledge, the model we have presented here is the first one that considers the dynamics of YAP spatial localization in conjunction with its activation through Rho-induced cellular tension. We base our work on a model in which the concentration of active Rho forms a polarized profile in response to localized stimuli [32], proposing a two-way coupling between YAP and Rho that implicitly accounts for the influence of mechanical stimuli on YAP activation. We consider several possible types of behaviours of the system that arise in different areas of parameter space, and analyze the model's predictions for the ratio of nuclear to cytoplasmic YAP ($R$), which is used as an experimental measure of YAP activation.

At fixed magnitudes of the mechanical stimulus ($q$) and strictly positive feedback of YAP on Rho, we predict that both Rho concentration and $R$ reach a steady value after the initial perturbation to Rho is applied. These stationary values lie on a sigmoidal curve that qualitatively reproduces experimental measurements of $R$ versus cell adhesive area [59].
At other values of the kinetic parameters that govern the chemical reactions in the system, in particular if the YAP-Rho coupling is stronger and allows for both positive and negative feedback, our model predicts that both \( R \) and the concentrations of the various components exhibit oscillatory behaviour. At both low and high \( q \), the system relaxes after a perturbation in Rho via damped oscillations, whereas at intermediate \( q \), the same perturbation gives rise to sustained oscillations.

The time scales for Rho activity oscillations that we predict agree in order of magnitude with earlier experiments \[60, 61\] and theory \[62\]. However, the period of the YAP oscillations that we predict at stationary \( q \) is of the order of seconds, which differs considerably from the fluctuations on the scale of hours reported by Franklin et al. \[63\]. The oscillations in the latter study are induced by oscillating calcium levels, which affect many processes other than mechanotransduction, and the discrepancy in time scales suggests that they are due to a mechanism different from the one we propose. The period of the oscillations we observe is dictated by the rate of change of the gradient in active Rho, which is determined by the balance between the rates of Rho production and diffusion. The diffusion coefficients of the active and inactive forms of RhoGTPases are known \[56\], and the data in Refs \[60–62, 70\] exhibits oscillations in RhoGTPase activity with a period of \( \sim 10 \) s, which is comparable to our results for the case with sustained oscillations in the Rho gradient. This suggests that the kinetic parameters we employ here are realistic if the Rho-YAP coupling takes the form that we assume. We thus believe that it would be intriguing to conduct an experimental study of the time scales and region of parameter space that we consider here and that such a study is necessary to establish whether the different regimes we predict exist in biological systems. Note, however, that the time scales in our 1D model could potentially be significantly different from those in a real 3D system because the assumption that the diffusion coefficient values measured in such systems may not apply to our 1D strip \[71, 72\]. Moreover, our 1D system requires all species diffusing from one end of the cell to the other to pass through the nucleus, whereas in a real cell they could move around it instead. With all these factors in mind and given both the absence of detailed quantitative data on the chemical reactions involved in the mechanotransduction pathway and the likely variability due to factors such as cell type, we do not attempt a more detailed analysis of the kinetic parameters for YAP and explore a range of values that yields several different dynamic regimes.

Several recent experimental studies have demonstrated other mechanisms of YAP regulation that could potentially lead to oscillations in YAP activity on time scales similar to the ones we predict. Kofler et al. \[35\] have shown that active nuclear export/import of TAZ is regulated by sequences known as nuclear efflux/localization signals (NES/NLS) within the protein that are also present in YAP, and that RhoA regulates the NES. Optogenetic manipulation of the NES/NLS of other transcription factors, e.g. myocardin-related transcription factor A has recently been shown to allow for their nuclear efflux/import on a timescale of several minutes, see \[73\]. Thus, it is in principle possible for YAP translocation to occur much faster than in the experiments of Franklin et al. \[63\]. Moreover, active transport via NES/NLS can be regulated in a variety of ways that do not require gene
transcription: NLS motives can be masked or blocked, e.g. via post-translational modification of either the NLS itself or of other parts of the molecule, see Ref. [74].

The key role of YAP nuclear export rates was also highlighted in a recent study by Ege et al. [75] that looked at YAP nuclear shuttling via fluorescence methods. Their work suggests that YAP dynamics is regulated by its rate of export from the nucleus, and that actin, Src-family kinases and exportin (XPO1) play an important role in controlling that rate. Notably, the characteristic times for nucleocytoplasmic EYFP–YAP translocation induced by various types of light-induced perturbations reported by Ege et al., are of the order of 10 s.

Optogenetic studies have also been performed on the mechanotransduction signalling pathway as well. Dowbaj et al. [76] have recently used a photo-responsive LOV-TRAP system to sequester YAP and TAZ to the cytoplasm or the mitochondrial surface and study their nuclear translocation. Notably, they observe characteristic times for YAP/TAZ export from the nucleus on the order of 10 s. Valon et al. [77] have employed a similar optogenetic system to sequester the RhoA activator ARHGEF11 between the plasma and mitochondrial membranes, thereby regulating cell contractility. Upon sequestering ARHGEF11 to one or the other membrane, they observed that traction forces and actin levels within cells changed within a time scale of several minutes after being optically stimulated. Concomitant changes in the amount of nuclear YAP occurred on a time scale of the order of 30 min, and it was possible to induce oscillations in this quantity by periodically switching the optical stimulus that regulated ARHGEF11 on and off.

Another mechanism for YAP regulation has been suggested by Gao et al. [78], who applied mechanical forces on cells through a thin sheet of PDMS. In contrast with Aureille et al. [22], who applied a local deformation to the nucleus, Gao et al. observed localization of YAP to the cytoplasm accompanied by F-actin depolymerization and RhoA downregulation. Intriguingly, Gao et al. also observed that LPAR1, a member of the G-protein coupled receptor (GPCR) family, which is known to regulate RhoGTPase activity [79], forms clusters on the cell membrane that are disrupted by both the application of a mechanical force and the actin polymerization inhibitor Cytochalasin D. Based on these observations, Gao et al. suggest that mechanical forces regulate YAP by controlling the level of F-actin and RhoA through LPAR1.

Note that, unlike the mechanism of YAP-Rho coupling via ARH GAP 28, ARHGAP 29, and NUA2 proposed by Mason et al. [40], pathways for YAP regulation through GPCRs and NES/NLS modification do not require transcription and can therefore act on time scales that are short compared with the several hours typical for the latter process. These experimental observations indicate that the discrepancy between the rates of the fastest experimentally observed processes involving YAP and our predictions is about one order of magnitude. Such a discrepancy can be eliminated with a different choice of parameters, which we have chosen not to do here because that would be of limited value in the absence of detailed experimental data.

Finally, we find that applying a time-dependent mechanical stimulus q to a system which for stationary q qualitatively reproduces experimental data for R versus adhesive area and only allows for positive YAP-Rho feedback results in a dependence of R on time that closely follows that of q.

Our model demonstrates that even a simplistic view of the chemical signalling pathway that governs cellular mechanotransduction can yield rich dynamic behaviour if mechanical stimuli are taken into account. The model qualitatively replicates existing experimental data for fixed values of the mechanical stimulus q and predicts oscillatory regimes that would be intriguing to study experimentally. This work is a first step in understanding how YAP activation and Rho signalling work together to enable cells to perceive their mechanical microenvironment. This is important because over the last decade YAP has emerged as the central signalling hub for mechanosensing and the Rho GTPase proteins have been established as key regulators of cytoskeletal dynamics. More importantly, mechanical activation of YAP through Rho signalling has been shown to play an important role in vital biological processes, from the expansion and survival of human embryonic stem cells [80] to viscoelastic feedback from the extracellular matrix that modulates proliferation and cancer metastasis [11]. It is, therefore, essential to construct spatiotemporal models of YAP mechanotransduction that allow for testable predictions. The framework presented in this study can easily be extended to 2D, which would allow for exploring the impact of more complex mechanical stimulation such as anisotropy in mechanical cues acting on the cells and the corresponding spatial distribution of YAP within the cells. Furthermore, establishing the spatiotemporal dynamics of YAP expression within the cell and its interconnection with the cell’s force-generating machinery is an important step towards building more cohesive models of cell motility and bridging the gap between mechanotransduction at the individual cell level and mechanical force generation by collective migration at the multicellular level.

AUTHOR CONTRIBUTIONS
J.K.N.: conceptualization, investigation, methodology, data curation, formal analysis, software, visualization, writing – original draft, writing – review & editing.
M.L.H.: conceptualization, visualization, writing – review & editing.
M.H.J.: conceptualization, writing – review & editing, resources, supervision, project administration, funding acquisition.
A.D.: conceptualization, writing – original draft, writing – review & editing, resources, supervision, project administration, funding acquisition.

SUPPLEMENTARY DATA
Supplementary data are available at INTBIO Journal online and at https://doi.org/10.17894/ucph.0006efd8-a7db-483a-892b-73c540046e55, where concentration profile data and the scripts for their generation and analysis are stored.

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