DEPARTMENT OF CHEMICAL ENGINEERING

INSTITUTE OF CHEMICAL TECHNOLOGY PRAGUE

LABORATORY OF MICROCHEMICAL ENGINEERING

Can Oscillatory Convection Accelerate Signal Propagation in Simple Epithelium?

COMSOL CONFERENCE ROTTERDAM 2013

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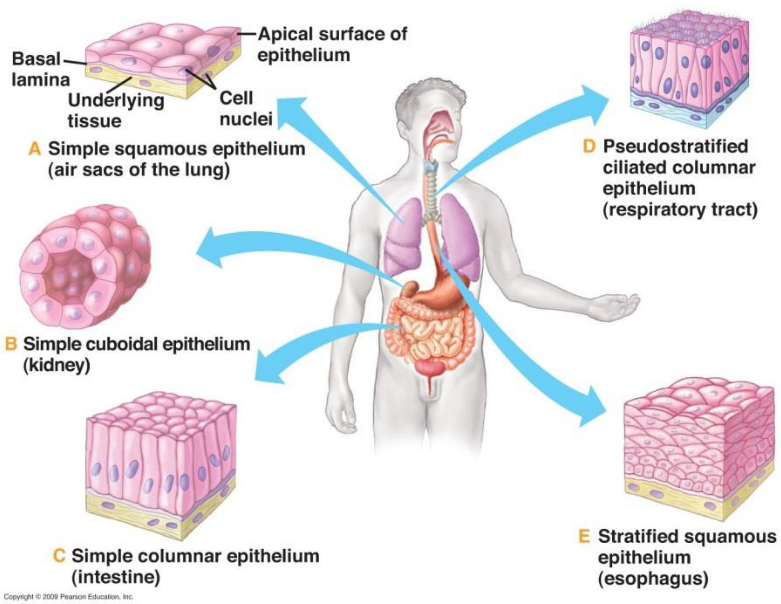
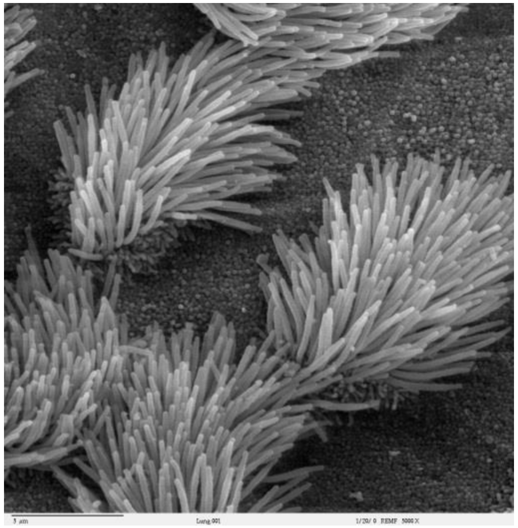
Epithelial cell communication

- Short distance signaling: extracellular ligand molecules + membrane receptors
- Growth factors + tyrosine kinase receptors
  - Proper combination: cell fate – proliferation, apoptosis, differentiation, etc.
    complex processes – wound healing and organ development
- Convective flow: formation of the left-right body axis, healing of vascular wounds, etc.

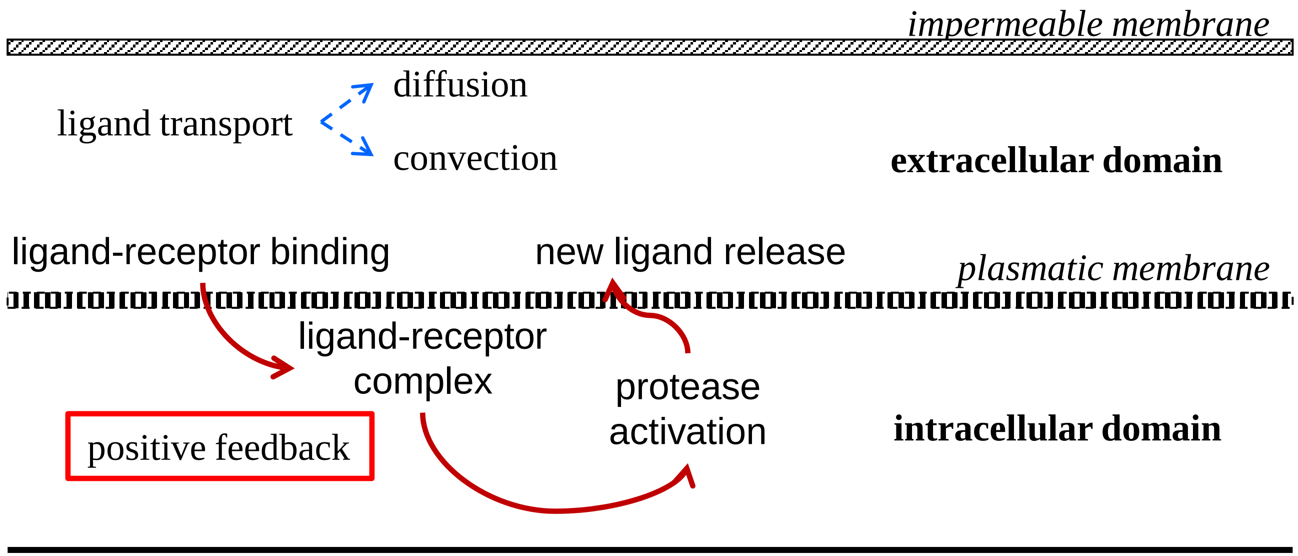


http://pharmaworld.pk.cws3.my-hosting-panel.com/products/gallery/gal753_t43.jpg

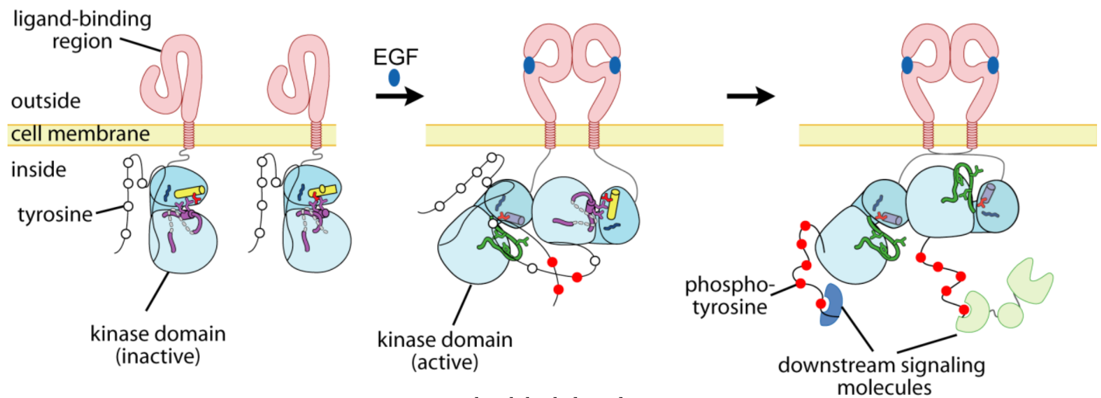


Respiratory epithelium of the trachea
cs.wikipedia.org

Positive feedback loop



EGFR activation



jkweb.berkeley.edu

Nonstationary convective flow

- Real systems – nonstationary convective flow
  - Heart action
  - Body movement
  - Circadian rhythm, etc.
- Two types of nonstat. convective flow:
  - Pulsatile flow
  - Oscillatory flow

http://www.economist.com/blogs/babbage/2012/08/obituary?fsrc=gn_ep

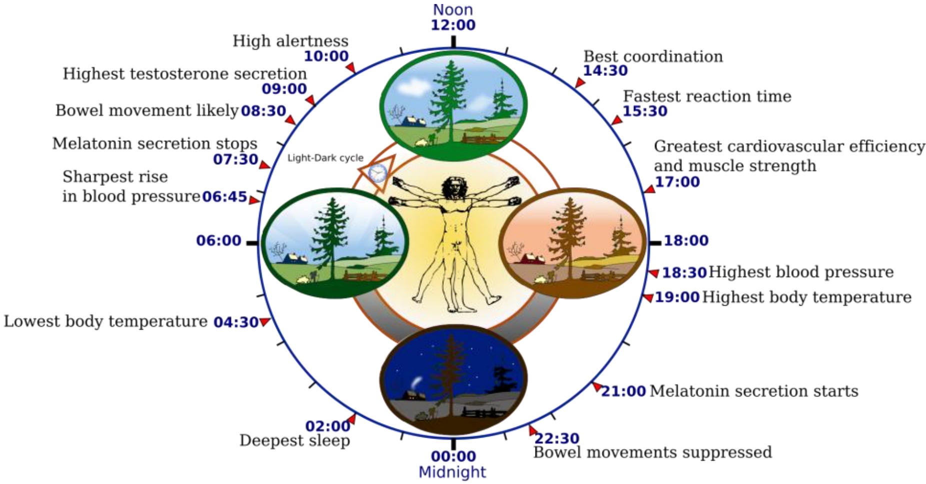
- Model takes oscillatory convective flow into account

$$v_x(t) = v_A \sin(2\pi f t)$$

v_A – amplitude of oscillations

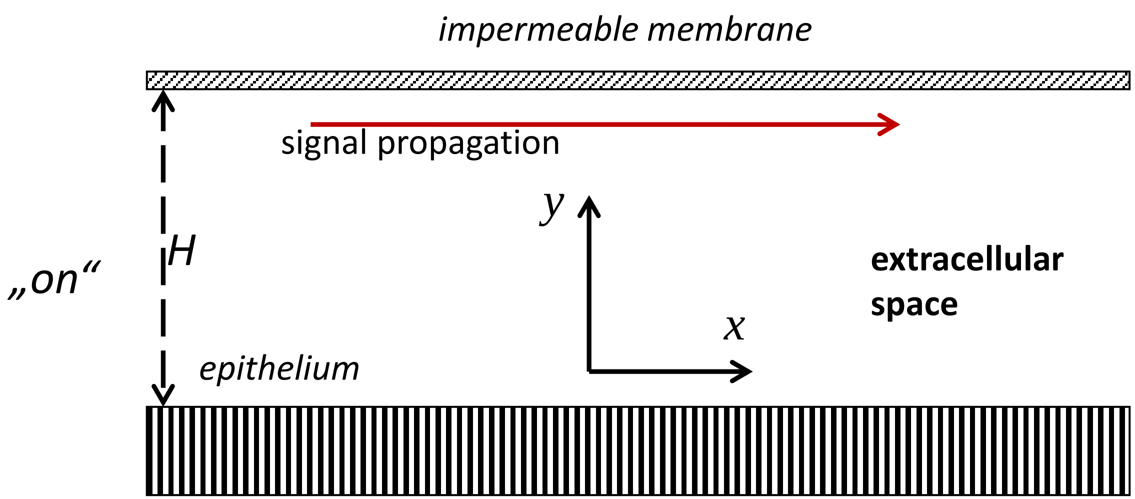
f – frequency of oscillations

t – time



wikipedia.org

Model definition



$$-D_S \left.\frac{\partial S}{\partial y}\right|_{y=H} = 0$$

$$-D_S \left.\frac{\partial S}{\partial y}\right|_{y=0} = -k_S^{on} SR + k_S^{off} C + g_S P$$

Ligands: $$\frac{\partial S}{\partial t} + v_x(t)\frac{\partial S}{\partial x} = D_S\left(\frac{\partial^2 S}{\partial x^2} + \frac{\partial^2 S}{\partial y^2}\right)$$

Receptors: $$\frac{\partial R}{\partial t} = Q_r - k_S^{on} SR + k_S^{off} C - k_R^e R$$

Protease: $$\frac{\partial P}{\partial t} = g_p \tilde{\sigma}(C) - k_p P$$

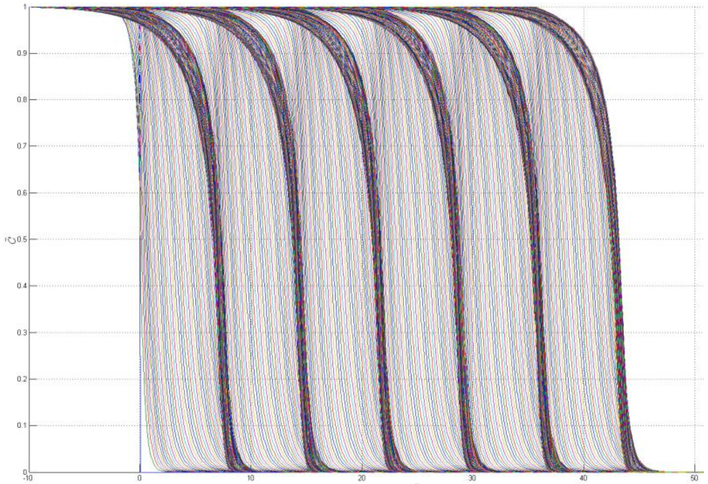
Ligand-receptor complexes: $$\frac{\partial C}{\partial t} = k_S^{on} SR - \left(k_S^{off} + k_C^e\right) C$$

- Ligands – PDE, general form
- Receptors, complexes and protease – weak form

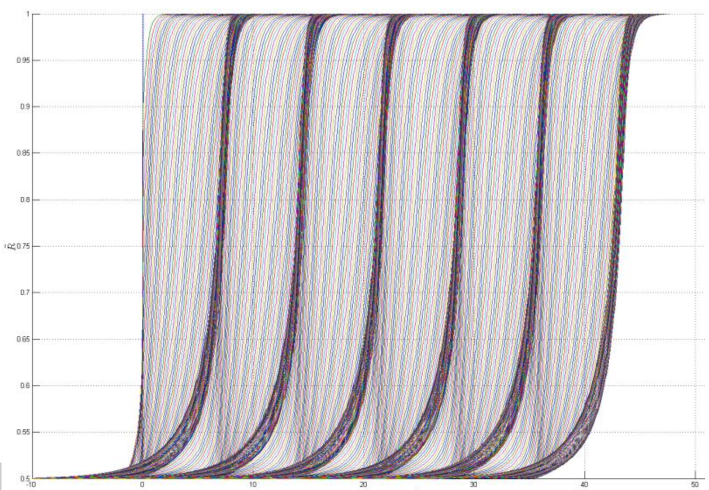
Simulations

- Dynamical simulations – COMSOL Multiphysics 3.5 interconnected with Matlab

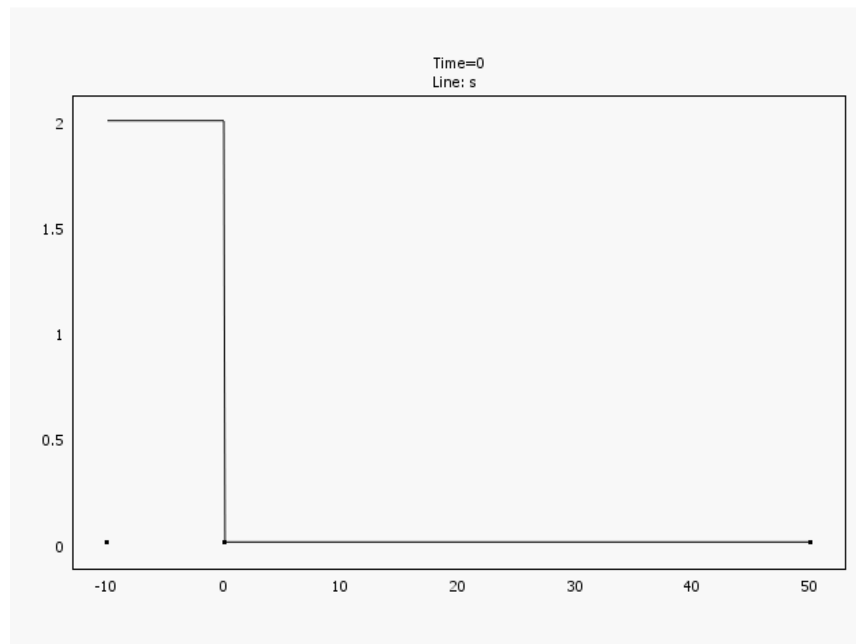
- Relative and absolute tolerances: $1{\cdot}10^{-4}$
- Uniform finite elements of size 0.01



All solutions for ligand-receptor complexes



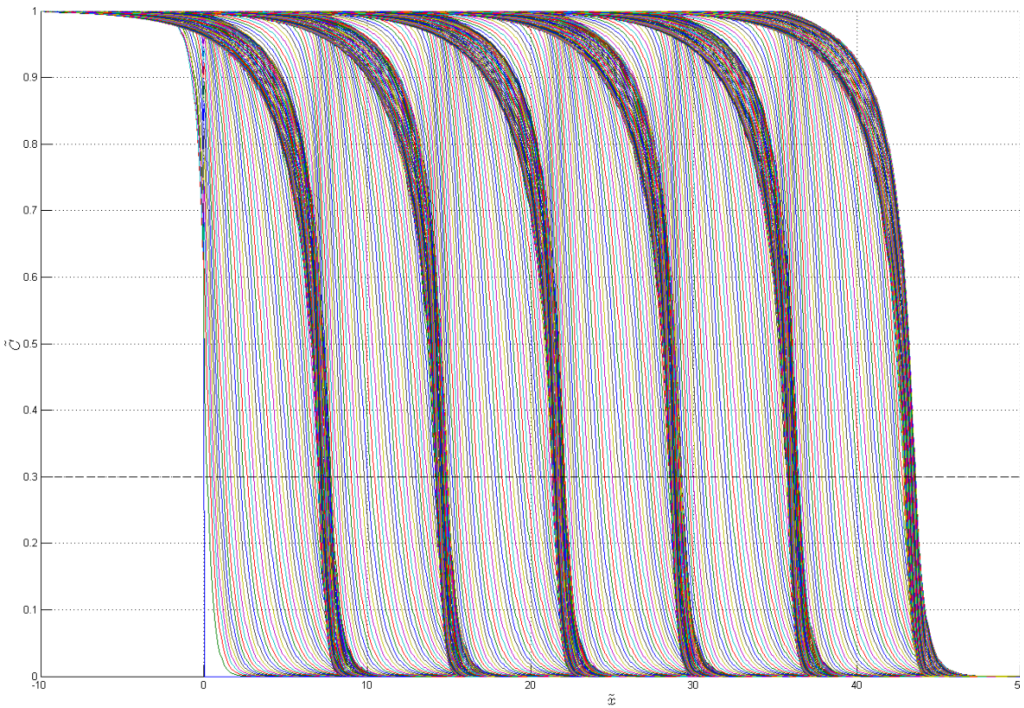
All solutions for free ligands



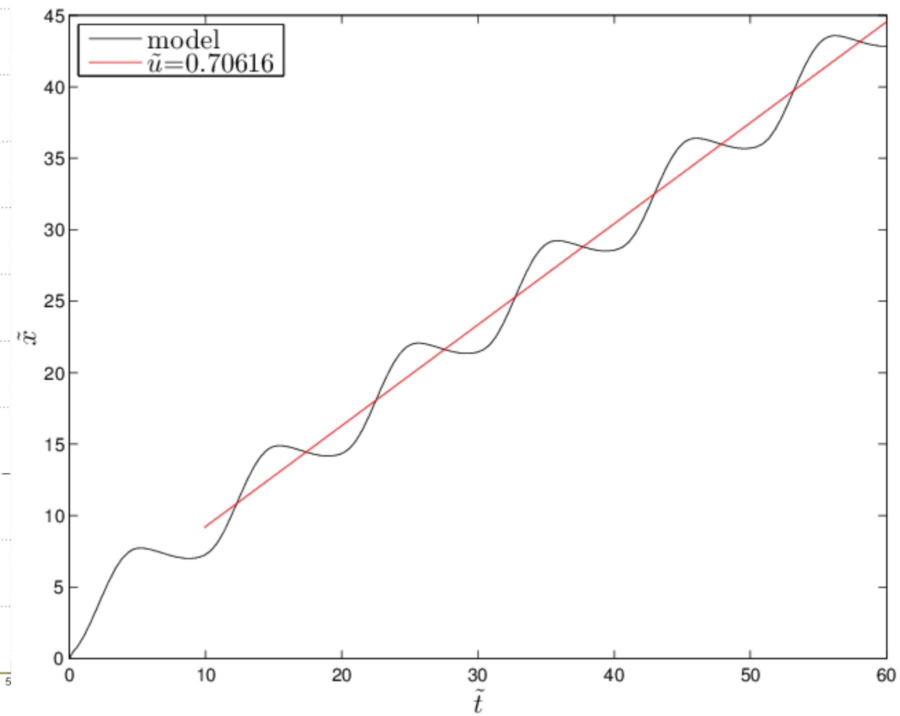
Ligand propagation

Evaluation of results

All solutions for ligand-receptor complexes



Evaluation of the averaged propagation velocity

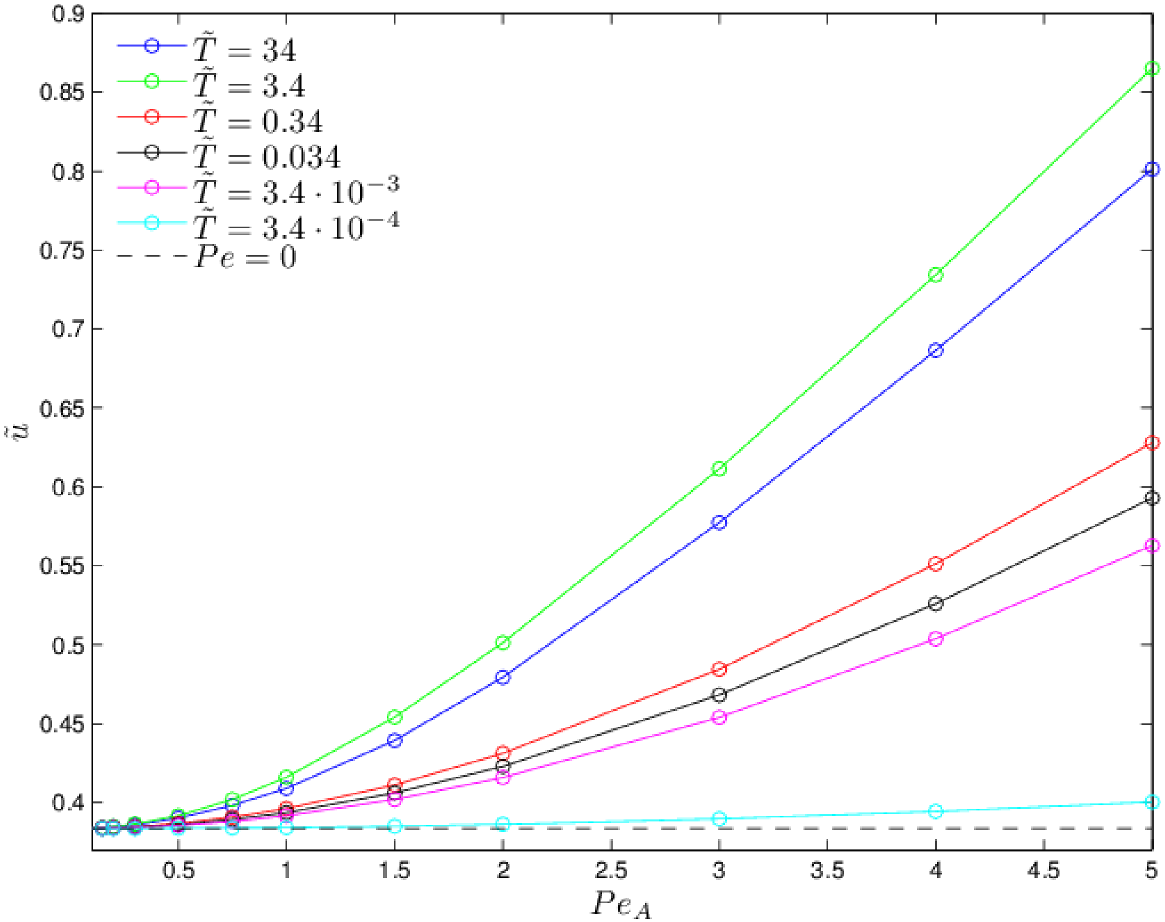


- The position of the concentration front in space evaluated at the concentration equal to the complex threshold $\tilde{C} = \tilde{C}_T$

$$\tilde{u} = d\tilde{x} / d\tilde{t}$$

Dependence of signaling velocity on amplitude

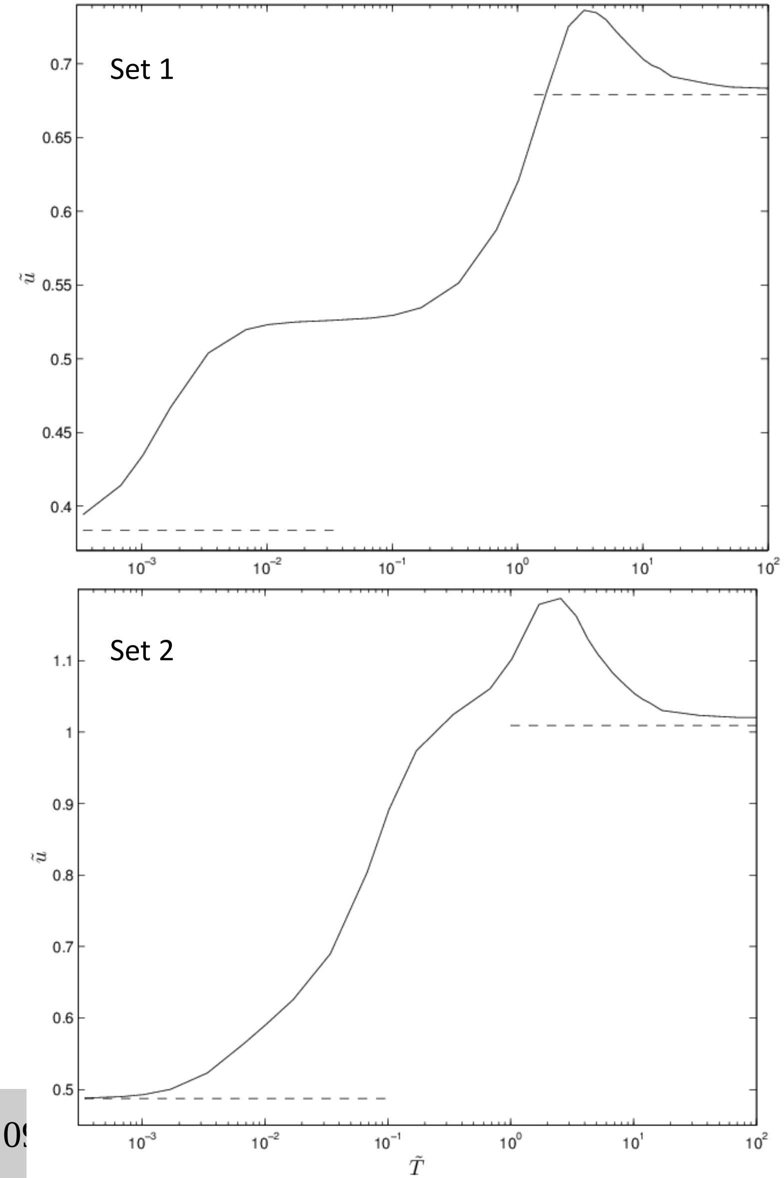
- Lower asymptote - velocity of the signal propagation in a system without the convective transport
- The velocity increase exceeds 100 % for suitable period of oscillations



Harmonic oscillations

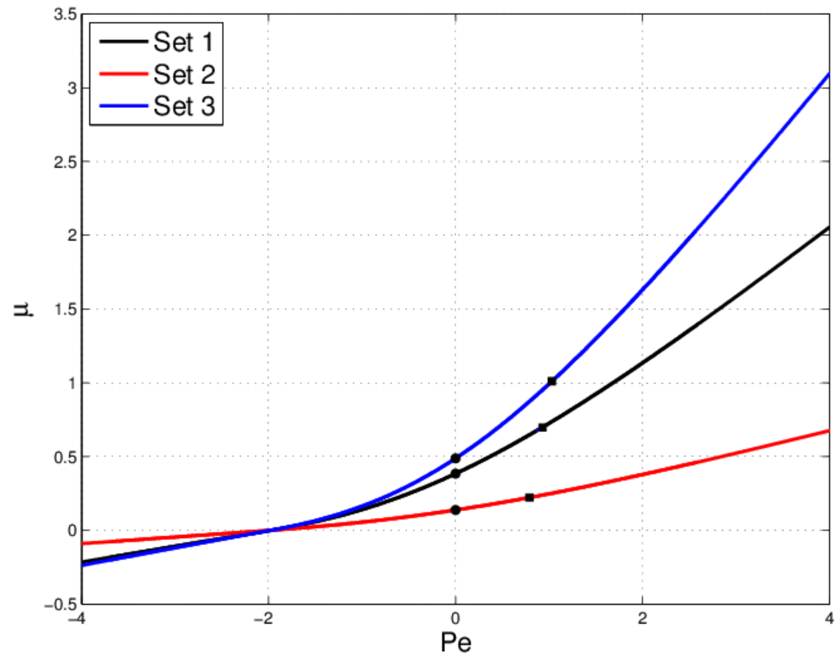
$$v_x(t) = v_A \sin(2\pi f t)$$

Dependence of signaling velocity on period



- Lower asymptote - propagation velocity in a system without the convective transport
  - attained when the fastest reaction process is ten times slower than the oscillatory flow period

Dependence on Péclet number for nonoscillating regimes



Conclusions

- The propagation velocity under the oscillatory flow is significantly higher than that under no convection case, up to 100 % in our study

- Dependence of the time averaged propagation velocity on the period of oscillations
  - Nonlinear, quite complex, several inflection points and a maximum
  - Upper and lower asymptotes

- Oscillatory convection can accelerate signal propagation in simple epithelium

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Dimensionless model

Constant velocity of convective transport

$$\tilde{\tau}_S \frac{\partial \tilde{S}}{\partial \tilde{t}} = -\tilde{v}_x \frac{\partial \tilde{S}}{\partial \tilde{x}} + \frac{\partial^2 \tilde{S}}{\partial \tilde{x}^2} + \frac{1}{\alpha^2} \frac{\partial^2 \tilde{S}}{\partial \tilde{y}^2}$$

$$\tilde{\tau}_R \frac{\partial \tilde{R}}{\partial \tilde{t}} = 1 - \tilde{R} + \gamma \left[(1 - \beta_S) \tilde{C} - \tilde{S}\tilde{R} \right]$$

$$\tilde{\tau}_C \frac{\partial \tilde{C}}{\partial \tilde{t}} = \tilde{S}\tilde{R} - \tilde{C}$$

$$\frac{\partial \tilde{P}}{\partial \tilde{t}} = -\tilde{P} + \sigma \left(\tilde{C} - \tilde{C}_T \right)$$

$$-\left.\frac{\partial \tilde{S}}{\partial \tilde{y}}\right|_{\tilde{y}=0} = \alpha \left[(1 - \beta_S) \tilde{C} - \tilde{S}\tilde{R} + \beta_S \tilde{P} \right] \qquad -\left.\frac{\partial \tilde{S}}{\partial \tilde{y}}\right|_{\tilde{y}=1} = 0$$

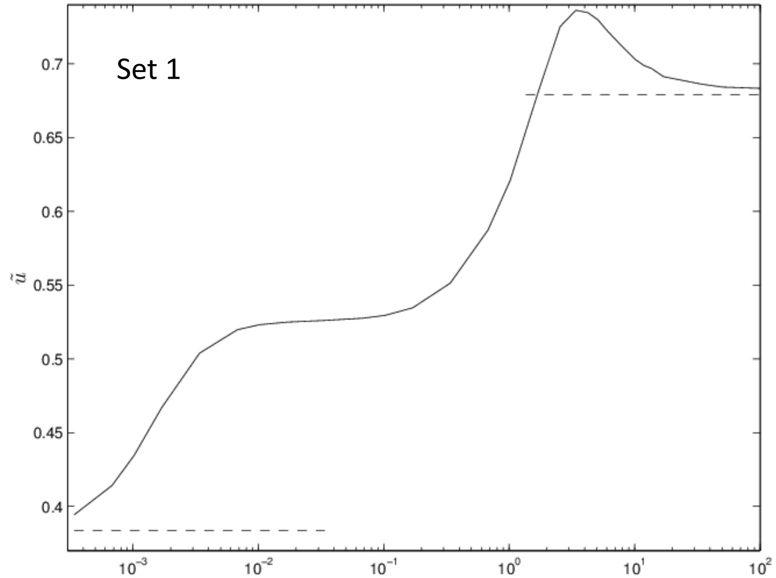
1D traveling wave model

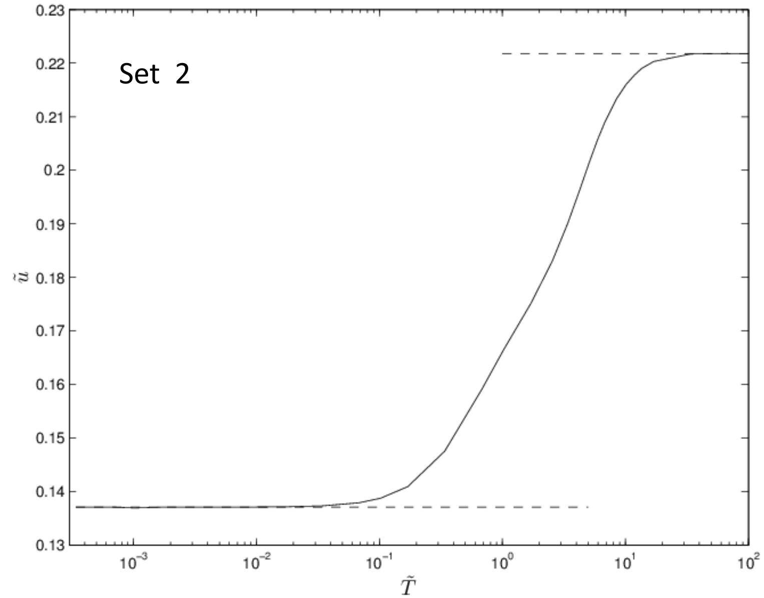
$$\xi \equiv \tilde{x} - \tilde{u}\tilde{t}$$

$$\frac{d^2 \hat{\tilde{S}}}{d\xi^2} + (\tau_S \tilde{u} - Pe) \frac{d\hat{\tilde{S}}}{d\xi} + \frac{1}{\alpha} \left[(1 - \beta_S)\tilde{C} - \hat{\tilde{S}}\tilde{R} + \beta_S \right] = 0 \qquad -\tilde{u}\tau_C \frac{d\tilde{C}}{d\xi} = \hat{\tilde{S}}\tilde{R} - \tilde{C}$$

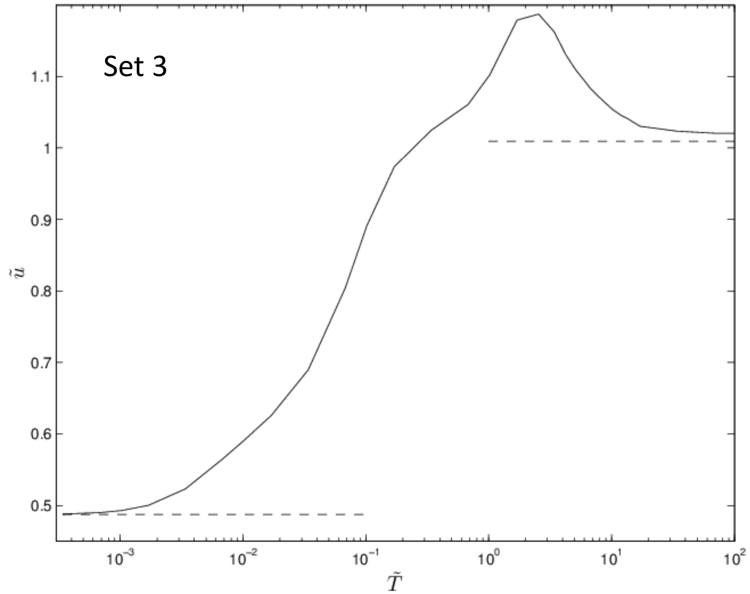
$$-\tilde{u}\tau_R \frac{d\tilde{R}}{d\xi} = 1 + \gamma \left[-\hat{\tilde{S}}\tilde{R} + (1 - \beta_S)\tilde{C} \right] - \tilde{R} \qquad -\tilde{u} \frac{d\tilde{P}}{d\xi} = \tilde{\sigma}(\tilde{C} - \tilde{C}_T) - \tilde{P}$$

Dependence of signaling velocity on period





Amplitude
Pe_A=4



Parameter	Set 1	Set 2	Set 3
$\alpha = HQ_R k_S^{on}/(k_R^e D_S) = y_0/x_0$	0.1	0.1	0.1
$\beta_S = k_C^e/(k_C^{off} + k_C^e)$	0.5	0.5	0.5
$\gamma = g_P g_S(k_S^{off} + k_C^e)/(k_P Q_R k_C^e)$	1	1	1
$\tilde{\delta} = \delta/C_0$	0.01	0.01	0.01
$\tau_C = k_P/(k_S^{off} + k_C^e)$	0.1	1	0.01
$\tau_R = k_P/k_R^e$	0.5	1	0.01
$\tau_S = k_R^{e2} D_S k_P/(Q_R k_S^{on})^2$	0.002	1	0.01
$\tilde{C}_T = C_T/C_0$	0.3	0.3	0.3
$\tilde{f}$	f/k_P	f/k_P	f/k_P