Mathematical models of the impact of heat shocks and Heat Shock Proteins on degenerative developments of biosystems

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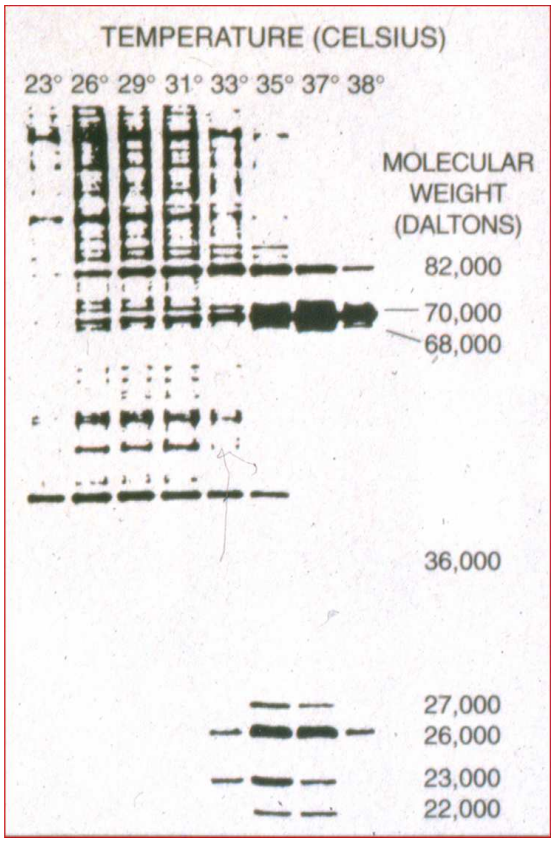
Mathematics for key technologies and innovation

Heat Shock Proteins (HSPs)



Tissiéres et al.1974

- HSPs are proteins whose synthesis increases under stress conditions.
- Induction of HSPs increases cell survival and stress-tolerance.
- Elevated expression of Hsp70 and Hsp90 in tumour cells has been detected in several cases
- HSPs prevent apoptosis induced by different cancer treatments, so these proteins can limit the efficacy of cancer therapy

Problems

Construction of the phenomenological generators of mathematical models for HSPs interventions:

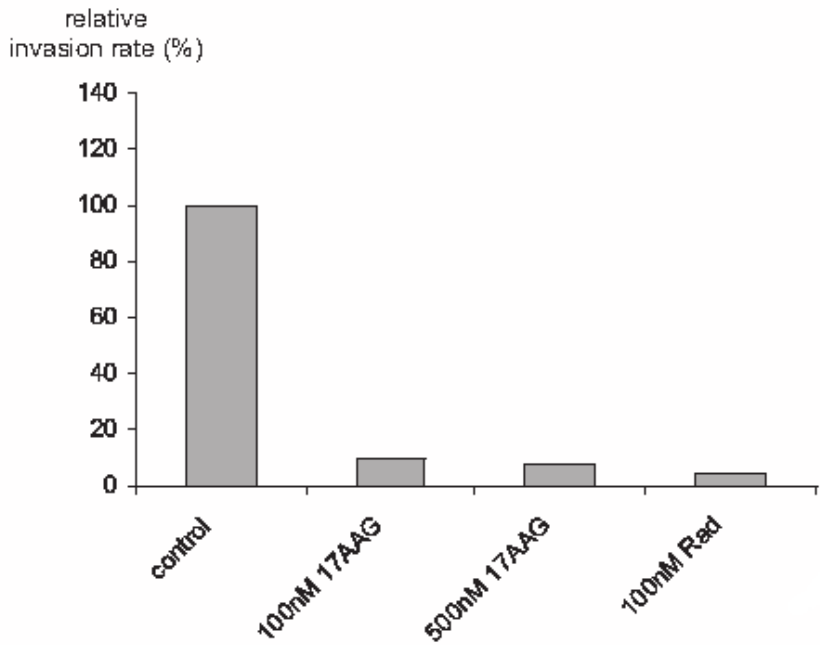
- iterative formulation and validation of interaction hypotheses
- support and guidance for designing experiments

Case Study Projects

(CS1) Dynamics of Heat Shock Proteins (Hsp70) under stress conditions

(CS2) The influence of Heat Shock Proteins (Hsp90) on cancer invasion of tissue

Cancer invasion



Inhibition of Hsp90 decreases cancer cells invasiveness.

Jakub Urbański (IIMCB).

Cancer invasion

(H1) Hsp90 regulates the activation of enzymes degrading the extracellular matrix (ECM) and, thus, reduced active Hsp90 concentration leads to impaired matrix degrading enzymes (MDE) activation.

Eustace at al. Functional proteomic screens reveal an essenstial extracellular role for hsp90α in cancer cell invasiveness Nat. Cell Biol. **6** 507-514 (2004).

(H2) Hsp90 affects the cytoskeleton. By influencing the cytoskeleton Hsp90 increases a cell's "flexibility" and, therefore, a decrease in active Hsp90 concentration leads to reduced cell migration.

Z. Szymańska, J. Urbański and A. Marciniak-Czochra "Mathematical modelling of the influence of heat shock proteins on cancer invasion of tissue", *J. Math. Biol.* to appear in 2008.

Cancer invasion model - hypothesis 1

Model with MDE activation (H1)

We assume that Hsp90 either directly activates or takes part in the production of the active form of some MDEs (like MMP2):

$$\frac{\partial u}{\partial t} = \underbrace{\nabla \cdot \left(D_u(u,v), \nabla u\right)}_{\text{random motility}} \underbrace{-\nabla \cdot \left(\chi(u,v)\, u\, \nabla v\right)}_{\text{haptotaxis}} \underbrace{+F(u,v)}_{\text{proliferation}}$$

$$\frac{\partial v}{\partial t} = \underbrace{-G(v,m)}_{\text{ECM degradation}}$$

$$\frac{\partial m}{\partial t} = \underbrace{D_m \nabla^2 m}_{\text{diffusion}} \underbrace{-\delta m}_{\text{degradation}} \underbrace{+J(u,v,h)}_{\text{activation}}$$

u - cancer cells, v - ECM, m - MDEs.

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Cancer invasion model - hypothesis 2

Model with variable cell flexibility

A decreased cell motility is probably the result of a poorer reorganisation of the cell cytoskeleton. In our model this means that $D_u(u,v,h)$ and $\chi(u,v,h)$ depend on Hsp90 concentration.

$$\frac{\partial u}{\partial t} = \underbrace{\nabla \cdot \left(D_u(u,v,h), \nabla u\right)}_{\text{random motility}} \underbrace{-\nabla \cdot \left(\chi(u,v,h)\, u\, \nabla v\right)}_{\text{haptotaxis}} \underbrace{+F(u,v)}_{\text{proliferation}}$$

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u - cancer cells, v - ECM, m - MDEs, h - Hsp90.

Cancer invasion model - hypothesis 2

Model with variable cell flexibility

We assumed that the random motility coefficient D_u and the haptotactic coefficient χ_u depend on the Hsp90 concentration h. Thus:

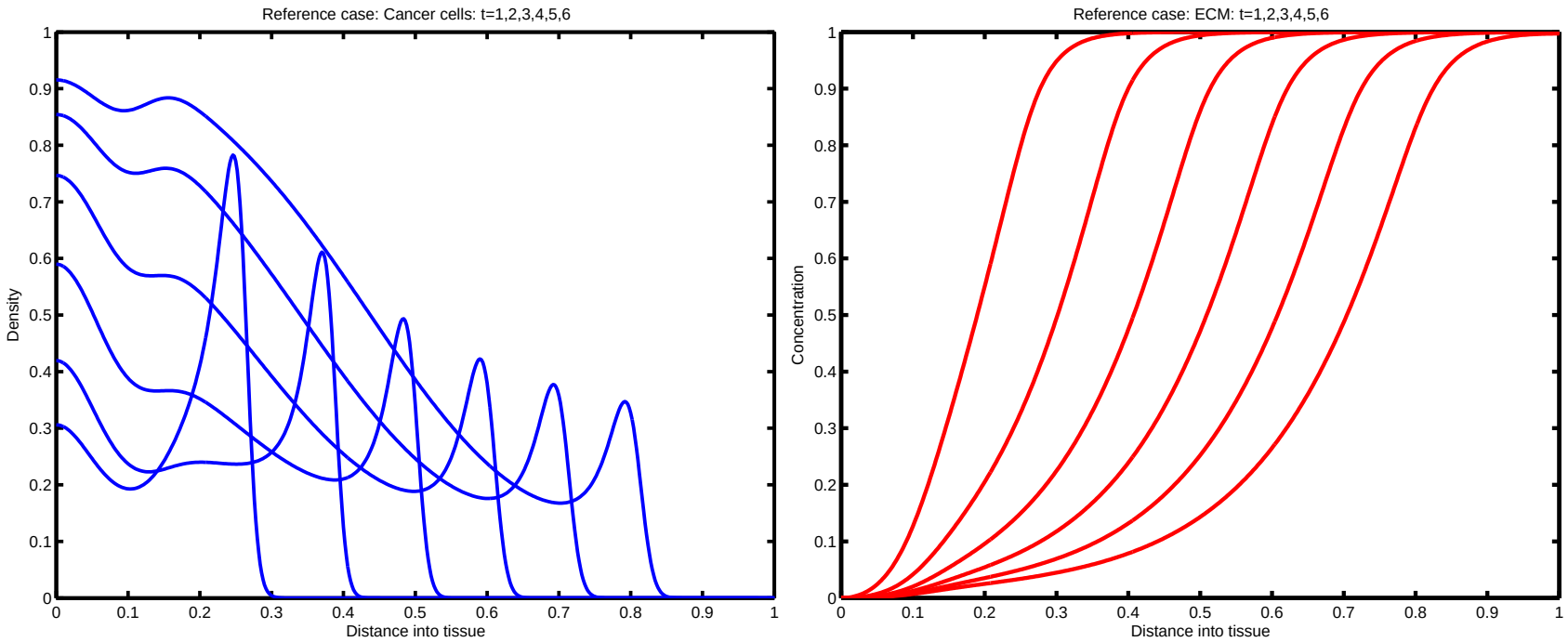
$$D_u(u,v,h) = D_u(u,v) \cdot I(h) \quad \text{and} \quad \chi_u(u,v,h) = \chi_u(u,v) \cdot I(h),$$

where $I(h)$ is an appropriate delay function.
In general, our distributed delay takes the following functional form:

$$I = \int_{-\infty}^{t} W(t-s)h(s)ds,$$

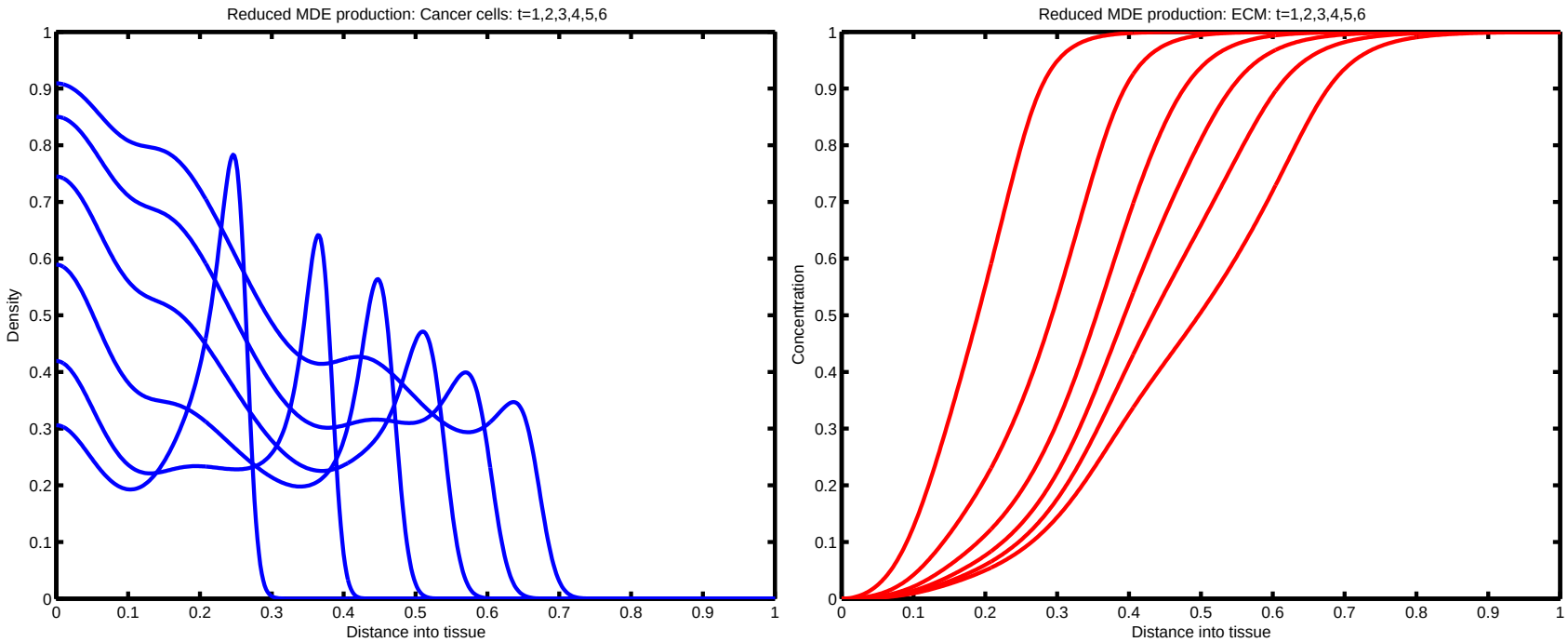
where $W(t-s)$ is the distributed delay kernel, which is a representation of how some past „memory” influences the present.

Computational Simulation Results: Control Case



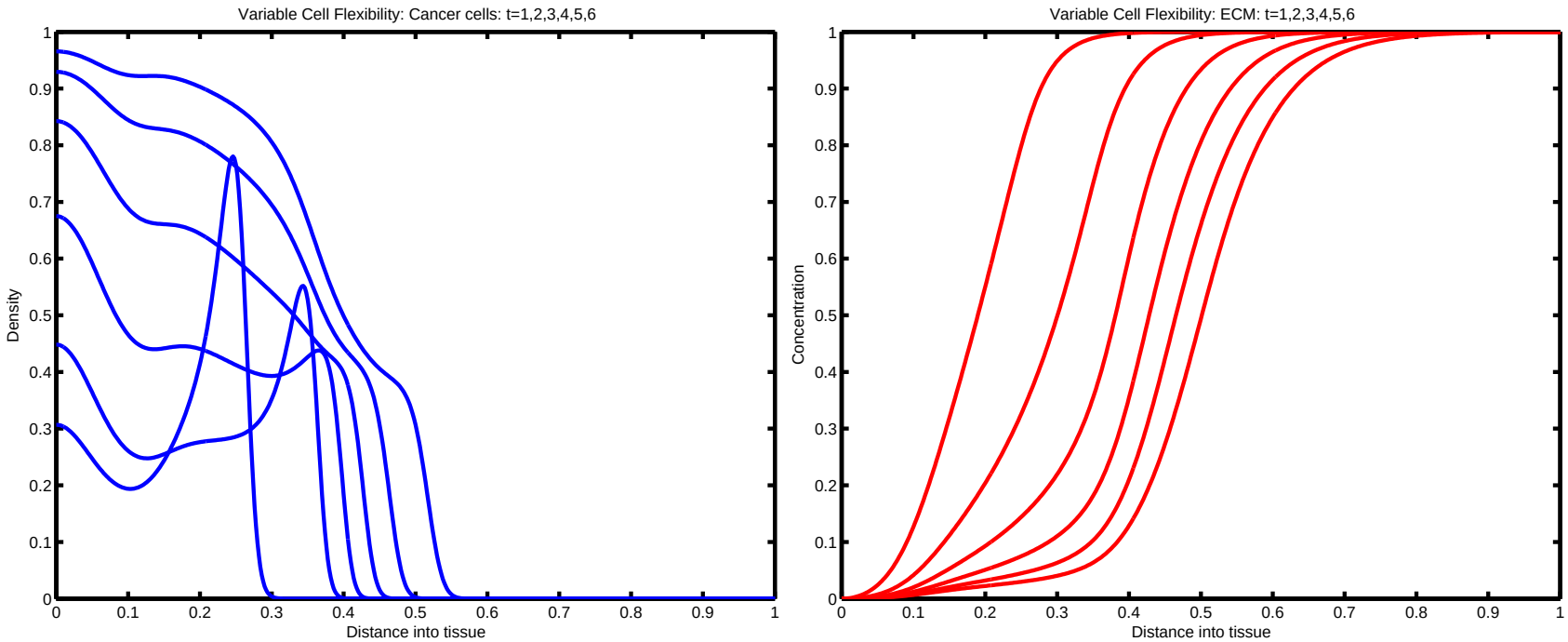
Plots showing the spatio-temporal evolution of the cancer cells (blue) and ECM (red) in reference case. The figures show an invading advancing front of cancer cells producing MDEs (not shown here), which then diffuse and degrade the ECM.

Reduced MDE activation (H1)



Plots showing the spatio-temporal evolution of the cancer cells (blue) and ECM (red) under the assumption that MDE production rate depends on active Hsp90 concentration.

Reduced flexibility (H2)

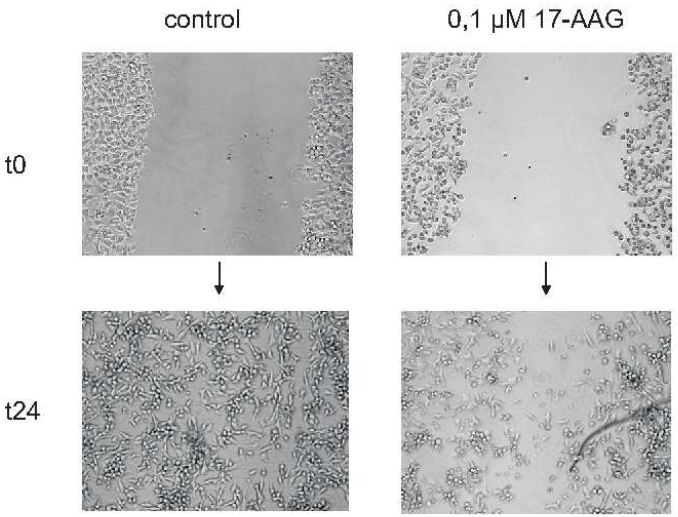


Plots showing the spatio-temporal evolution of the cancer cells (blue) and ECM (red) under the assumption that a cell's flexibility depends on active Hsp90 concentration.

Summary

- In both cases, inhibition of Hsp90 led to a decrease of the speed of the invasive wave of cancer cells and also to a reduced depth of penetration of the ECM by the cancer cells.
- The difference in the depth of invasion between the model with Hsp90-dependent MDE activation and the model with Hsp90-dependent cell flexibility is significant.
- Collectively all our data suggest that the role of Hsp90 in cancer cell invasion is linked to the mediation of the cell motility rather than control of MDE activation and secretion.

In vitro experimental results



Jakub Urbański (IIMCB).

Hsp90 inhibitors significantly reduce cancer cell invasion in a Matrigel assay, and to a lesser extent (but still significantly) reduce cell motility in a scratch assay. The second hypothesis obtained additional experimental evidence.

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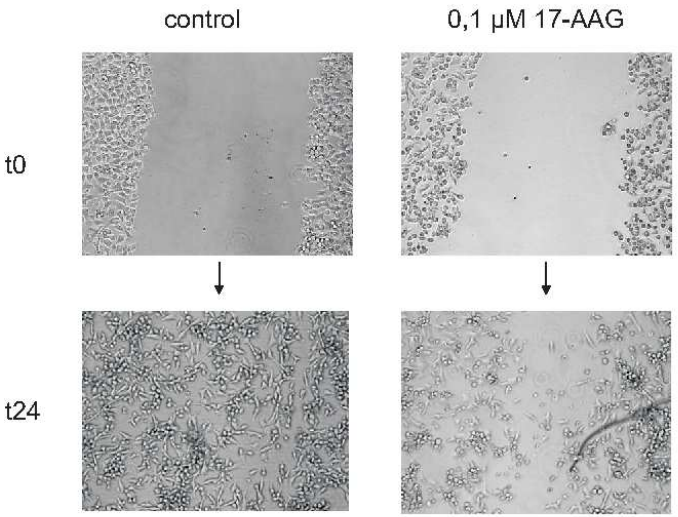

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Conclusions

Mathematical modelling

- helps to understand the key mechanisms of complex biological systems;
- makes experimentally testable predictions/hypotheses;
- helps to give indications for further experiments;
- can be used as a predictive tool for the initial efficient pre-testing of experiments i.e. „optimising” the order/schedule of future experiments;
- may be used in future as a replacement for many animal models („in silico” replaces „in vivo”).