Optimization of spatiotemporal control for systems described by cellular automata

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Outline

- Inspiration
- Adjoint sensitivity analysis
- Adjoint sensitivity analysis for cellular automata
- Numerical results
- Conclusion

Inspiration

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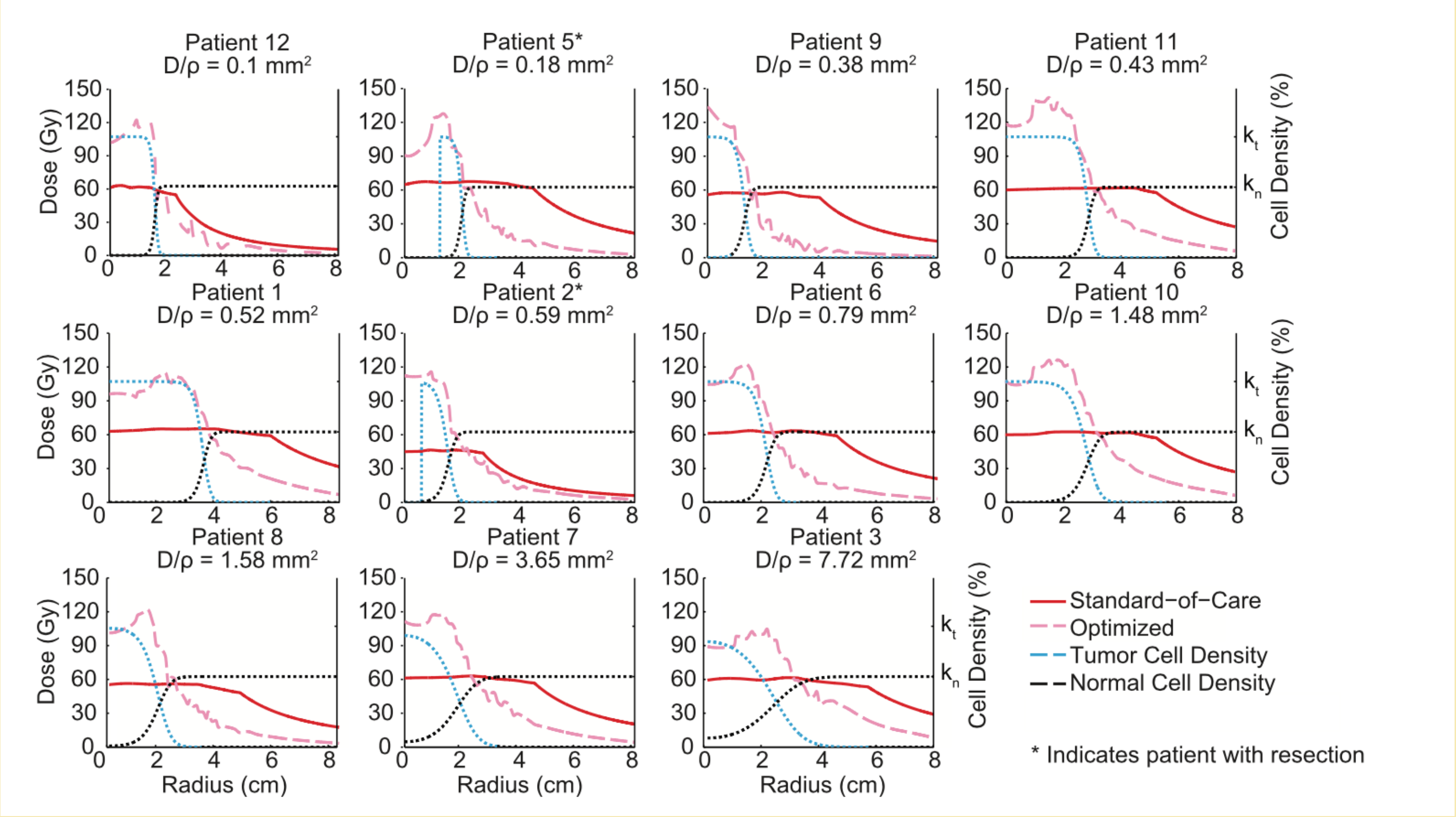
PLOS ONE

Toward Patient-Specific, Biologically Optimized Radiation Therapy Plans for the Treatment of Glioblastoma

David Corwin[1], Clay Holdsworth[2,3], Russell C. Rockne[1], Andrew D. Trister[2,4], Maciej M. Mrugala[5], Jason K. Rockhill[2], Robert D. Stewart[2], Mark Phillips[2], Kristin R. Swanson[1,6]*



Structural sensitivity analysis for discrete-time systems

$$M: \quad \begin{cases} x(t+1) = f(x(t), u(t)) \\ y(t) = g(x(t), u(t)) \end{cases} \qquad t = 0, 1, \ldots, T$$

$$x(t) \in R^n, u(t) \in R^m, y(t) \in R^q$$

$$x(0) = x_0, \quad u(t) = u_{nom}(t) \quad \rightarrow \quad x(t) = x_{nom}(t), \quad y(t) = y_{nom}(t)$$

Input-output sensitivity function

$$M: \quad \begin{cases} x(t+1) = f(x(t), u(t)) \\ y(t) = g(x(t), u(t)) \end{cases} \qquad t = 0,1,\ldots,T$$

$$u(t) = u_{nom}(t), \quad x(t) = x_{nom}(t)$$

$$S_{u_j(t_1)}^{y_i(t_2)} \overset{\text{df}}{=} \left. \frac{\partial y_i(t_2)}{\partial u_j(t_1)} \right|_{\substack{u_{nom}(t) \\ x_{nom}(t)}}, \qquad t_1, t_2 = 0,1,\ldots,T$$

$$S_{u(t_1)}^{y(t_2)} \overset{\text{df}}{=} \begin{bmatrix} \frac{\partial y_1(t_2)}{\partial u_1(t_1)} & \cdots & \frac{\partial y_1(t_2)}{\partial u_m(t_1)} \\ \vdots & \ddots & \vdots \\ \frac{\partial y_q(t_2)}{\partial u_1(t_1)} & \cdots & \frac{\partial y_q(t_2)}{\partial u_m(t_1)} \end{bmatrix}_{\substack{u_{nom}(t) \\ x_{nom}(t)}}, \; t_1, t_2 = 0,1,\ldots,T$$

Sensitivity model

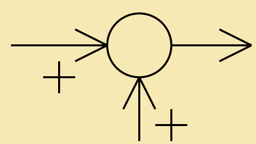
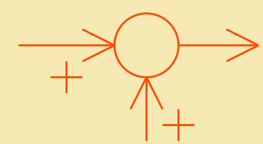
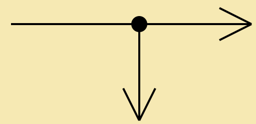
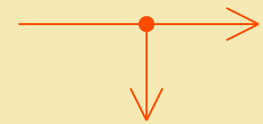
$$M: \quad \begin{cases} x(t+1) = f\big(x(t), u(t)\big) \\ y(t) = g\big(x(t), u(t)\big) \end{cases} \qquad t = 0,1,\ldots,T$$

$$\bar{M}: \quad \begin{cases} \bar{x}(t+1) = A(t)\bar{x}(t) + B(t)\bar{u}(t) \\ \quad \bar{y}(t) = C(t)\bar{x}(t) + D(t)\bar{u}(t) \end{cases}, \quad t = 0,1,\ldots,T$$

$$A(t) = \left.\frac{\partial f(\cdot)}{\partial x(t)}\right|_{\substack{u_{nom}(t) \\ x_{nom}(t)}} \qquad B(t) = \left.\frac{\partial f(\cdot)}{\partial u(t)}\right|_{\substack{u_{nom}(t) \\ x_{nom}(t)}}$$

$$C(t) = \left.\frac{\partial g(\cdot)}{\partial x(t)}\right|_{\substack{u_{nom}(t) \\ x_{nom}(t)}} \qquad D(t) = \left.\frac{\partial g(\cdot)}{\partial u(t)}\right|_{\substack{u_{nom}(t) \\ x_{nom}(t)}}$$

Structural sensitivity model

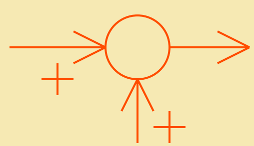
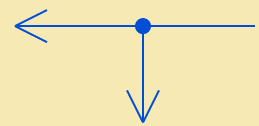
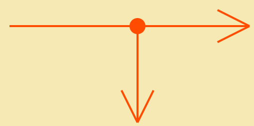
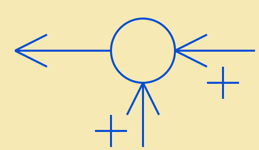
Element of the original block diagram		Element of the structural sensitivity model
Linear dynamic element	$\to \boxed{K(z)} \to$	$\to \boxed{K(z)} \to$
Linear static element	$\to \boxed{A} \to$	$\to \boxed{A} \to$
Nonlinear static element	$\xrightarrow{u} \boxed{f(u)} \to$	$\to \boxed{H(t)} \to \quad H(t) = \left.\frac{\partial f(\cdot)}{\partial u}\right\|_{u=u(t)}$
Summing junction		
Branching node		

Modified adjoint system

$$\bar{M}: \quad \begin{cases} \bar{x}(t+1) = A(t)\bar{x}(t) + B(t)\bar{u}(t) \\ \bar{y}(t) = C(t)\bar{x}(t) + D(t)\bar{u}(t) \end{cases}$$

$$\hat{M}: \quad \begin{cases} \hat{x}(t+1) = A^T(T-t)\hat{x}(t) + C^T(T-t)\hat{u}(t) \\ \hat{y}(t) = B^T(T-t)\hat{x}(t) + D^T(T-t)\hat{u}(t) \end{cases}$$

Adjoint system – the structural form

Element of the structural sensitivity model	Element of the modified adjoint system
$\rightarrow \boxed{K(z)} \rightarrow$	$\leftarrow \boxed{K^T(z)} \leftarrow$
$\rightarrow \boxed{A} \rightarrow$	$\leftarrow \boxed{A^T} \leftarrow$
$\rightarrow \boxed{H(t)} \rightarrow$	$\leftarrow \boxed{H^T(T-t)} \leftarrow$
	
	

The property of the adjoint system

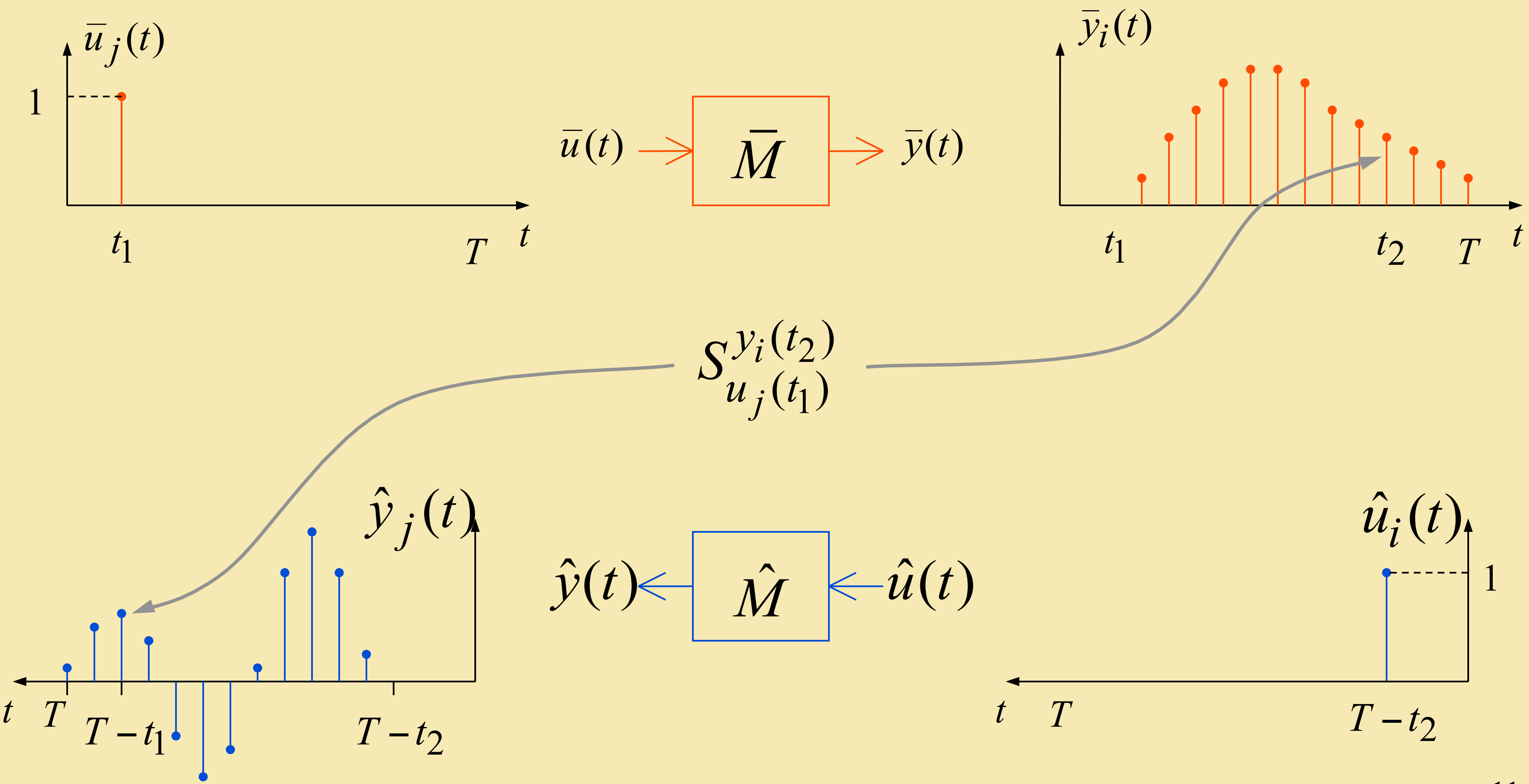
$$\bar{u}(t) \rightarrow \boxed{\bar{M}} \rightarrow \bar{y}(t) \qquad\qquad \hat{y}(t) \leftarrow \boxed{\hat{M}} \leftarrow \hat{u}(t)$$

$$\bar{y}(t) = \sum_{\tau=0}^{t} \bar{K}(t,\tau)\bar{u}(\tau) \qquad\qquad \hat{y}(t) = \sum_{\tau=0}^{t} \hat{K}(t,\tau)\hat{u}(\tau)$$

$$\bar{K}(t_2,t_1) = \hat{K}^T(T-t_1,T-t_2) = S_{u(t_1)}^{y(t_2)}(u_{nom},x_{nom})$$

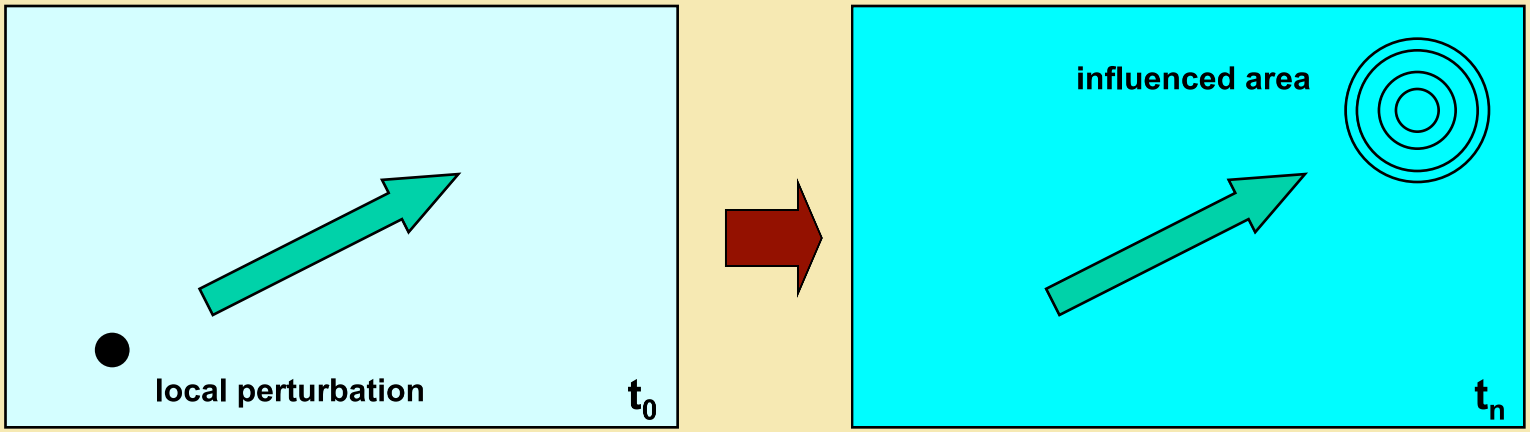
The input-output sensitivity is the Green function (pulse response) of the sensitivity model OR the adjoint system

The property of the adjoint system



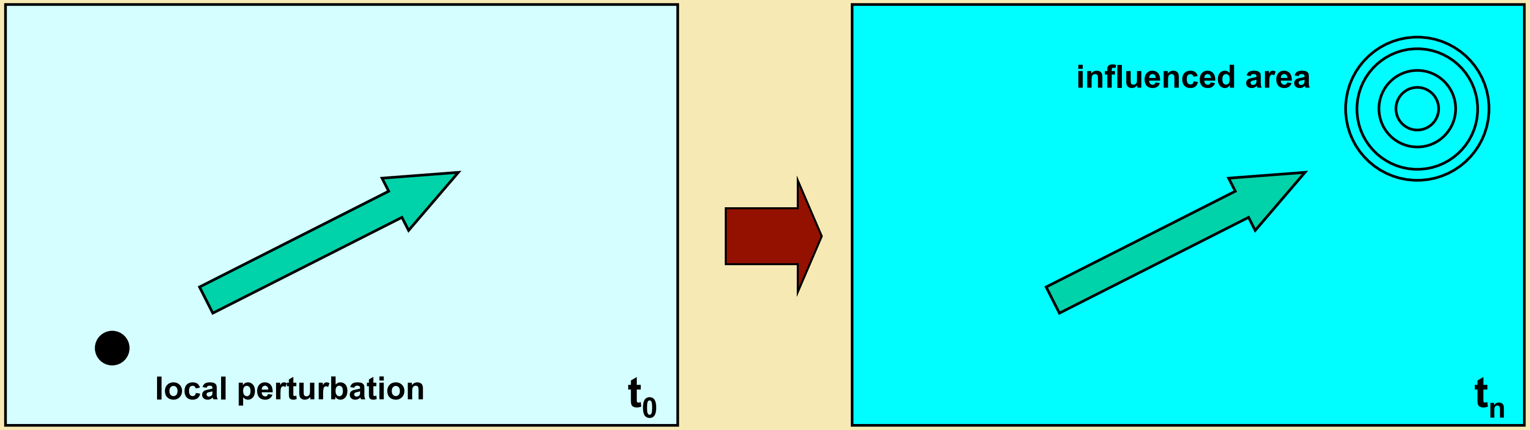
Forward vs. Adjoint Sensitivity Analysis

Forward Model

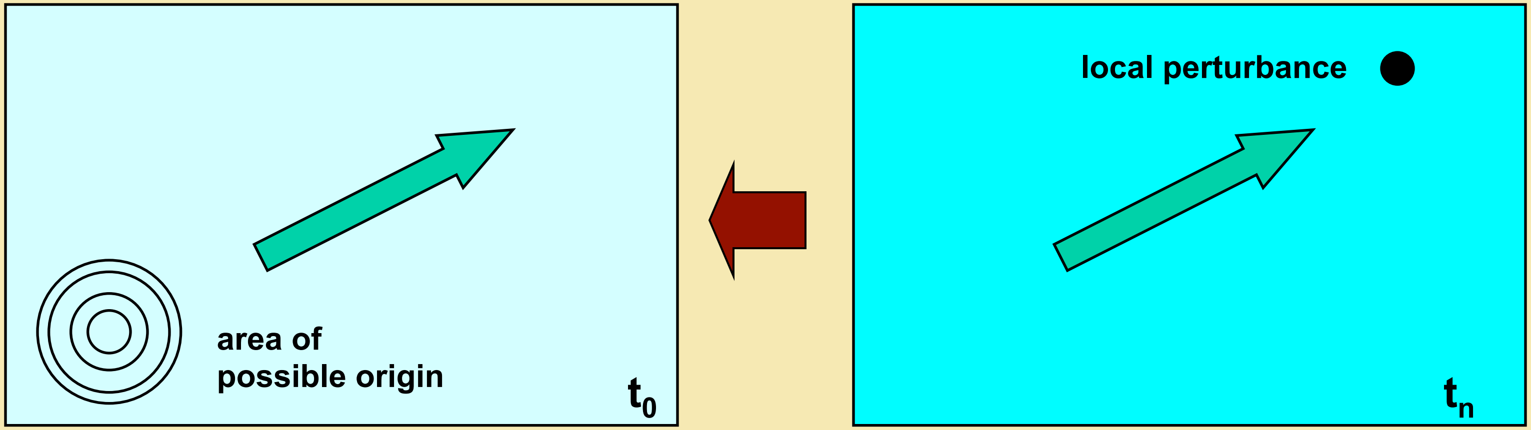


Forward vs. Adjoint Sensitivity Analysis

Forward Model



Adjoint Model



Application of the adjoint sensitivity analysis for different models and problems

Hybrid continuous-discrete systems

Fujarewicz K, Galuszka A: *Generalized backpropagation through time for continuous time neural networks and discrete time measurements.* Artificial Intelligence and Soft Computing - ICAISC 2004 (eds. L. Rutkowski, J. Siekmann, R. Tadeusiewicz and L. A. Zadeh), Lecture Notes in Computer Science, **2004**, 3070, p. 190-196

Parameter estimation for ODE systems

Fujarewicz K, Kimmel M, Swierniak A: *On fitting of mathematical models of cell signaling pathways using adjoint systems.* Mathematical Biosciences and Engineering, **2005**, 2(3), p. 527-534

Fujarewicz K, Kimmel M, Lipniacki T, Swierniak A: *Adjoint systems for models of cell signaling pathways and their application to parameter fitting.* IEEE-ACM Transactions On Computational Biology and Bioinformatics, **2007**, 4(3), p. 322-335

Kumala S, Fujarewicz K, Jayaraju D, Rzeszowska-Wolny J, Hancock R: *Repair of DNA Strand Breaks in a Minichromosome In Vivo: Kinetics, Modeling, and Effects of Inhibitors.* Plos One, **2013**, 8(1), p. 1-12

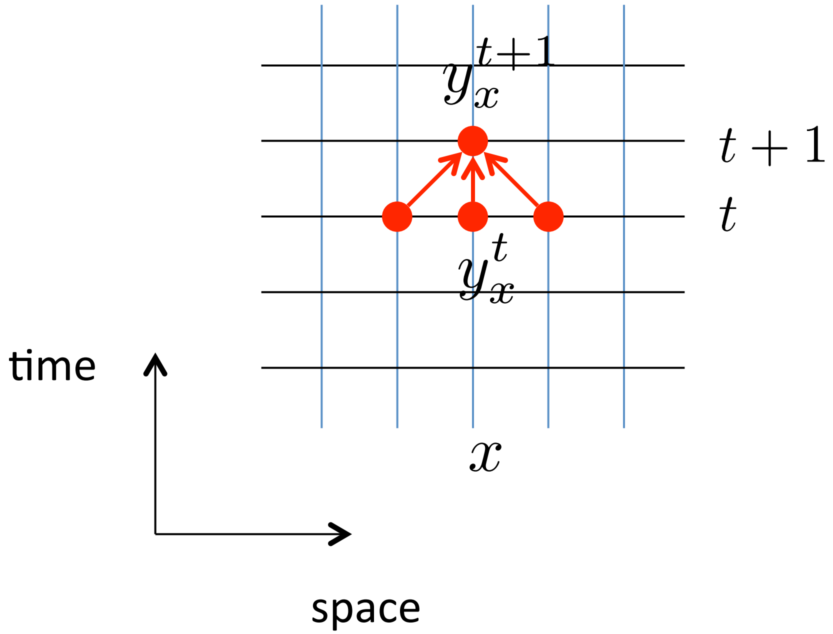
Łakomiec K, Kumala S, Hancock R, Rzeszowska-Wolny J, Fujarewicz K: *Modeling the repair of DNA strand breaks caused by γ-radiation in a minichromosome* . Physical Biology, **2014**, 11(4), p. 1-8

Parameter estimation for systems with delays (DDE)

Fujarewicz K, Łakomiec K: *Parameter estimation of systems with delays via structural sensitivity analysis* . Discrete and Continuous Dynamical Systems-series B, **2014**, 19(8), p. 2521-2533

Structural sensitivity analysis for cellular automata

Cellular automaton 1D with continuous state
(corresponds to finite difference method for PDE models)



Difference scheme

$$y_x^{t+1} = f(y_x^t, y_{x-1}^t, y_{x+1}^t, u_x^t)$$

u_x^t - local (in time and space) input

$t = 0, 1, 2, \ldots, t_{max}$

$x = 1, 2, 3, \ldots, x_{max}$

Objective function $$J = g(y_1^{t_{max}}, y_2^{t_{max}}, \ \dots \ , y_{x_{max}}^{t_{max}})$$

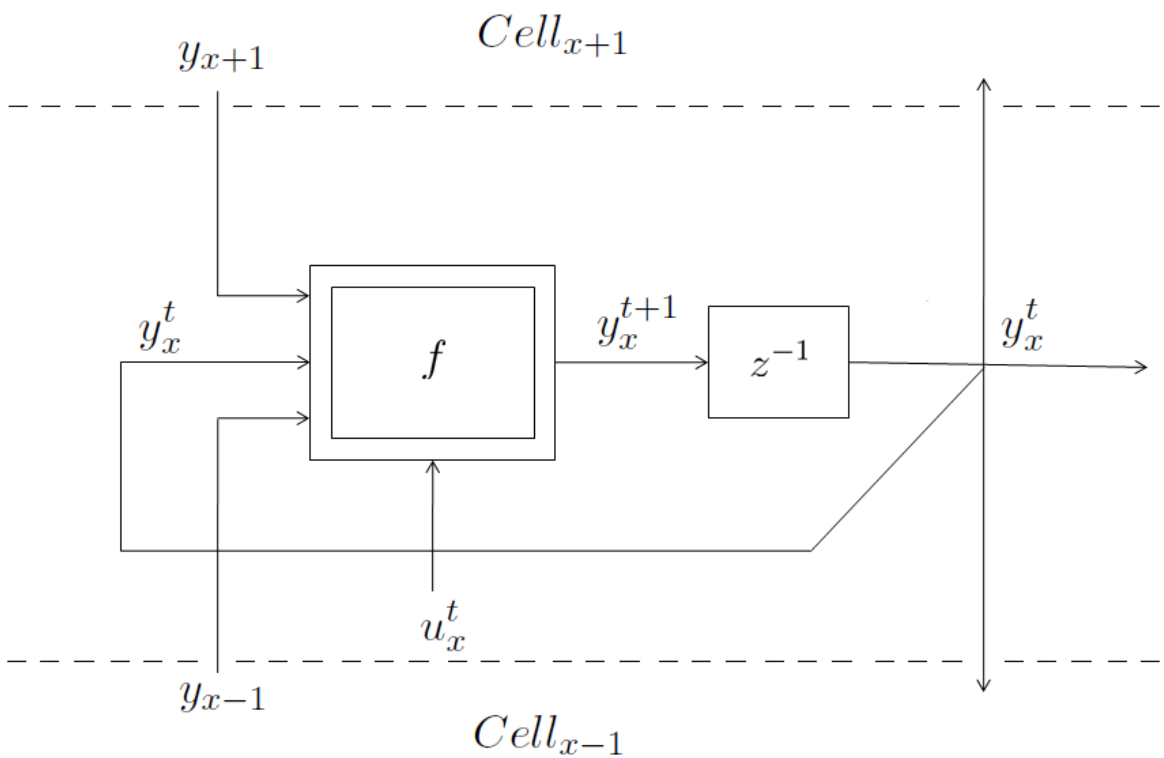
Matrix of the whole spatiotemporal control

$$U = \begin{bmatrix} u_1^1 & \dots & \dots & \dots & u_1^{t_{max}} \\ \vdots & \ddots & & & \vdots \\ \vdots & & u_x^t & & \vdots \\ \vdots & & & \ddots & \vdots \\ u_{x_{max}}^1 & \dots & \dots & \dots & u_{x_{max}}^{t_{max}} \end{bmatrix}$$

Searched spatiotemporal gradient of the objective function

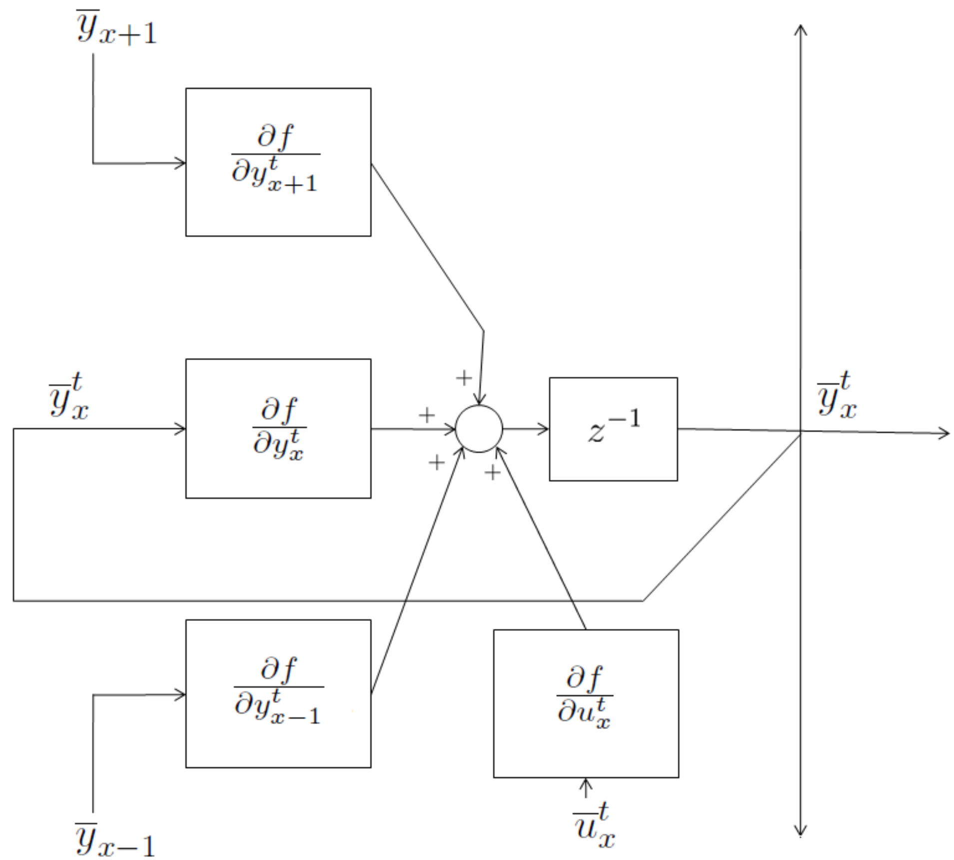
$$G = \nabla_U J = \begin{bmatrix} \frac{\partial J}{\partial u_1^1} & \dots & \dots & \dots & \frac{\partial J}{\partial u_1^{t_{max}}} \\ \vdots & \ddots & & & \vdots \\ \vdots & & \frac{\partial J}{\partial u_x^t} & & \vdots \\ \vdots & & & \ddots & \vdots \\ \frac{\partial J}{\partial u_{x_{max}}^1} & \dots & \dots & \dots & \frac{\partial J}{\partial u_{x_{max}}^{t_{max}}} \end{bmatrix}$$

Block diagram of one cell of the cellular automaton



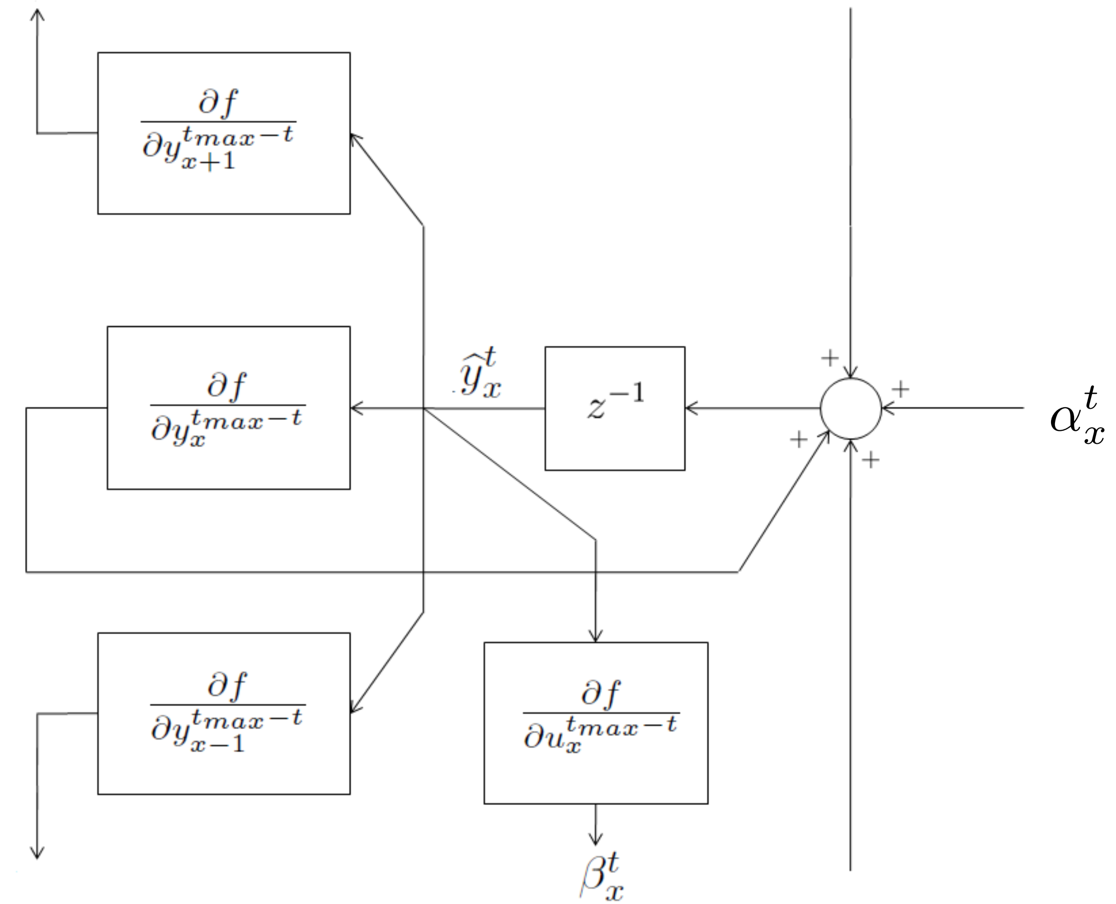
$$y_x^{t+1} = f(y_x^t, y_{x-1}^t, y_{x+1}^t, u_x^t)$$

The sensitivity model of one cell



$$\bar{y}_x^{t+1} = \left(\frac{\partial f}{\partial y_x}\right)_x^t \cdot \bar{y}_x^t + \left(\frac{\partial f}{\partial y_{x-1}}\right)_x^t \cdot \bar{y}_{x-1}^t + \left(\frac{\partial f}{\partial y_{x+1}}\right)_x^t \cdot \bar{y}_{x+1}^t + \left(\frac{\partial f}{\partial u}\right)_x^t \cdot \bar{u}_x^t$$

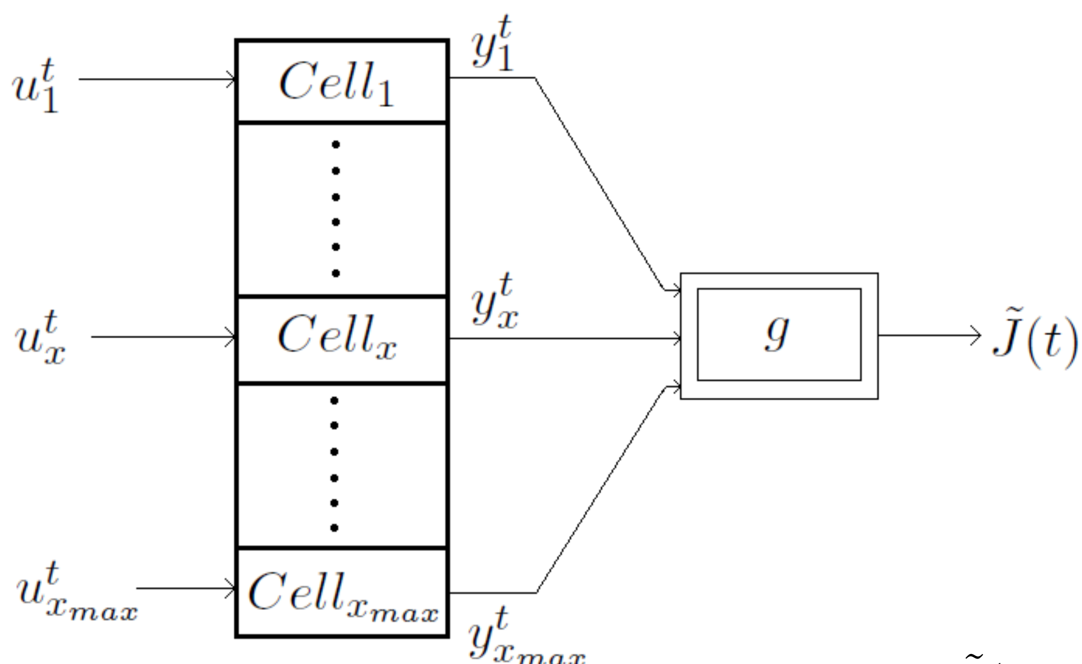
The adjoint model of one cell



$$\hat{y}_x^{t+1} = \left(\frac{\partial f}{\partial y_x}\right)_x^{t_{max}-t} \cdot \hat{y}_x^t + \left(\frac{\partial f}{\partial y_{x+1}}\right)_{x-1}^{t_{max}-t} \cdot \hat{y}_{x-1}^t + \left(\frac{\partial f}{\partial y_{x-1}}\right)_{x+1}^{t_{max}-t} \cdot \hat{y}_{x+1}^t + \alpha_x^t$$

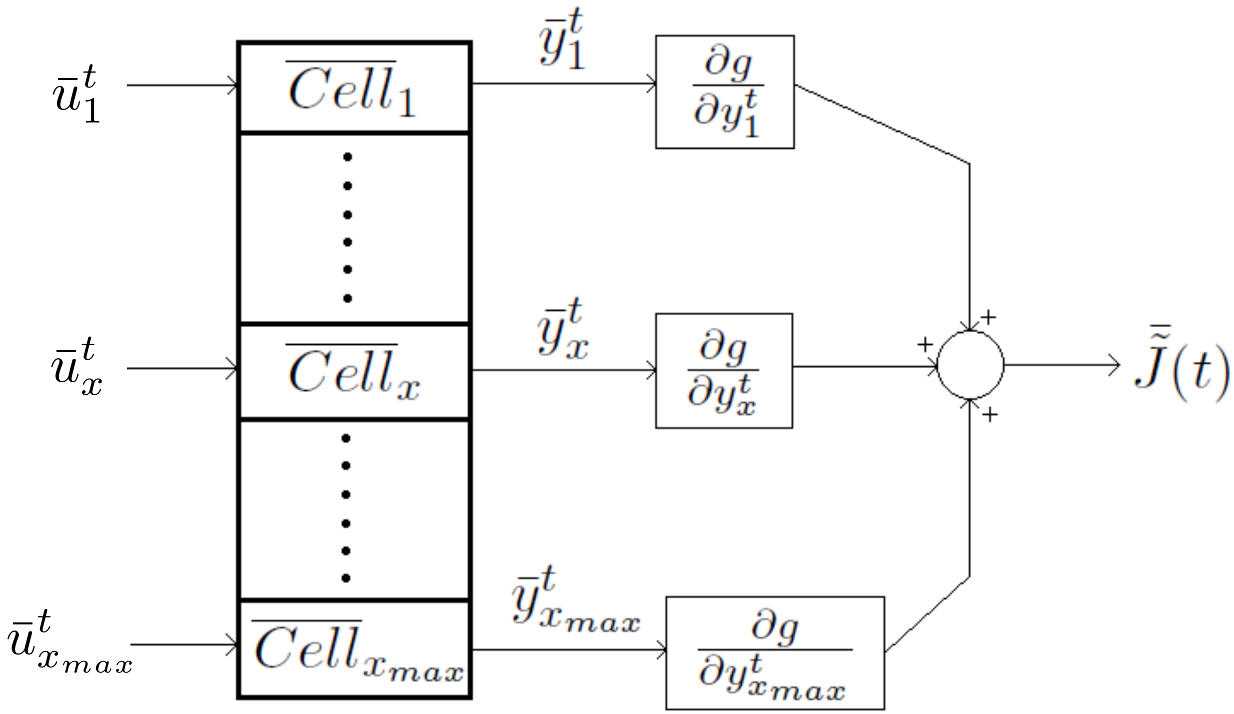
The cellular automaton with the block calculating the objective function

$$J = g(y_1^{t_{max}}, y_2^{t_{max}}, \ \dots \ , y_{x_{max}}^{t_{max}})$$

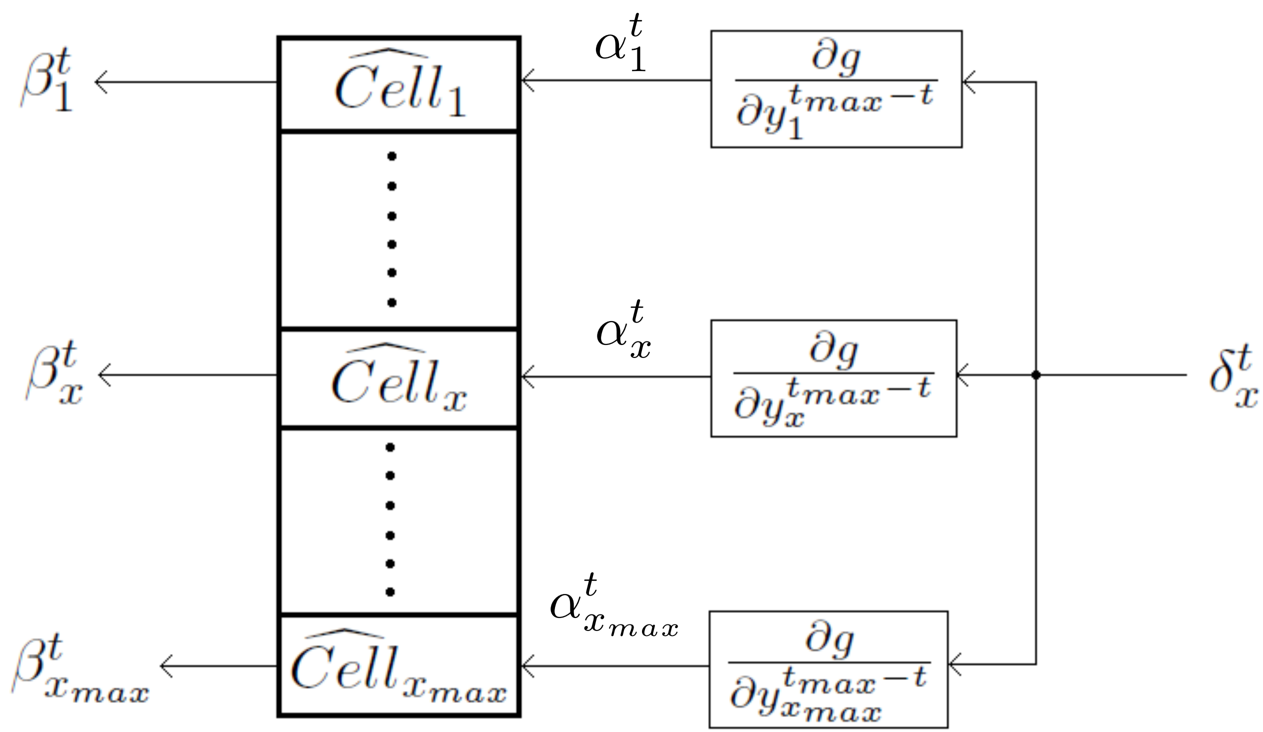


$$J = \tilde{J}(t_{max})$$

The sensitivity model



The adjoint model



The spatiotemporal gradient of the objective function.

$$\frac{\partial J}{\partial u_x^t} = \beta_x^{t_{max}-t}$$

$$G = \nabla_U J = \begin{bmatrix} \beta_1^{t_{max}} & \cdots & \cdots & \cdots & \beta_1^0 \\ \vdots & \ddots & & & \vdots \\ \vdots & & \beta_x^{t_{max}-t} & & \vdots \\ \vdots & & & \ddots & \vdots \\ \beta_{x_{max}}^{t_{max}} & \cdots & \cdots & \cdots & \beta_{x_{max}}^0 \end{bmatrix}$$

PDE model of tumor growth (Corwin et al. 2013)

$$\frac{\partial c}{\partial t} = \nabla \cdot (D \nabla c) + \rho c \left(1 - \frac{c}{k_t}\right) - R \cdot c \left(1 - \frac{c}{k_t}\right)$$

D	diffusion coefficient
ρ	proliferation coefficient
k_t	carrying capacity
$R = (1 - e^{-\alpha d - \beta d^2})$	radiation influence (LQ model)

PDE model of tumor growth (Corwin et al. 2013)

$$\frac{\partial c}{\partial t} = \nabla \cdot (D \nabla c) + \rho c \left(1 - \frac{c}{k_t}\right) - R \cdot c \left(1 - \frac{c}{k_t}\right)$$

D diffusion coefficient

ρ proliferation coefficient

k_t carrying capacity

$R = (1 - e^{-\alpha d - \beta d^2})$ radiation influence (LQ model)

Discretized model (difference scheme)

$$\frac{c_x^{t+1} - c_x^t}{\Delta t} = D \frac{c_{x-1}^t - 2c_x^t + c_{x+1}^t}{(\Delta x)^2} + (\rho - R) c_x^t \left(1 - \frac{c_x^t}{k_t}\right)$$

Optimized performance index: number of cancer cells at final time

$$J = \sum_{x=1}^{x_{max}} c_x^{t_{max}}$$

Constraints

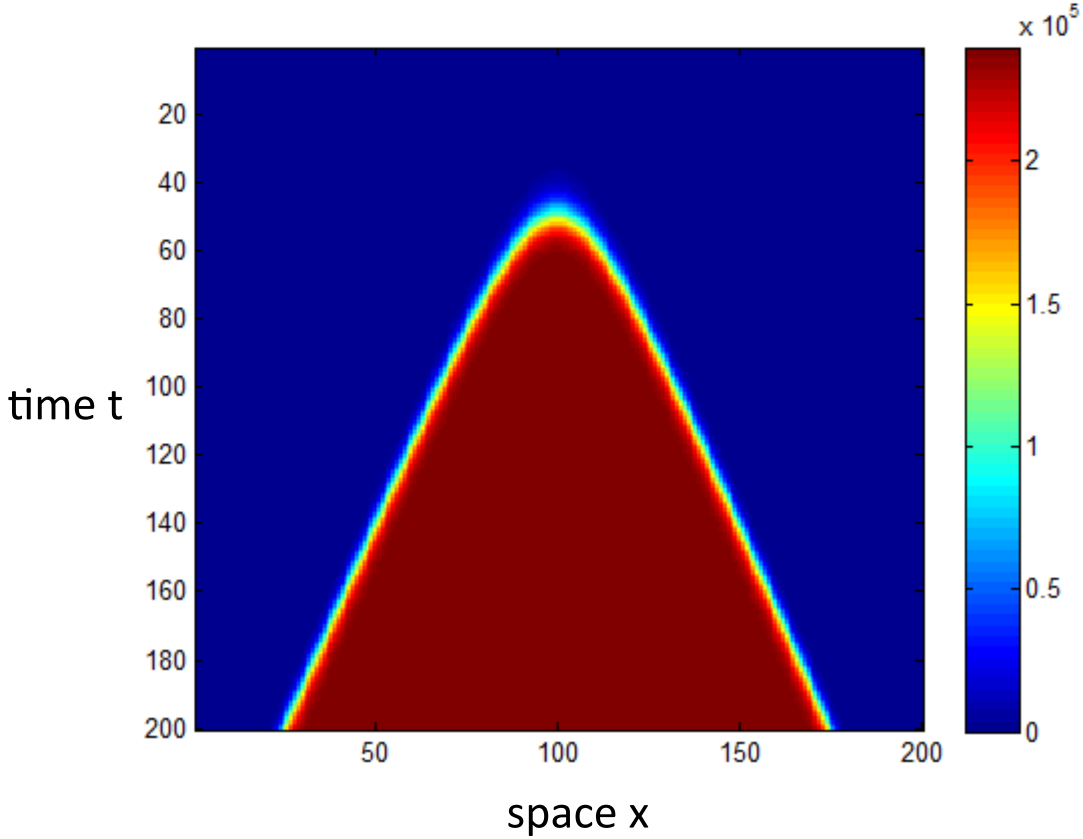
for total dose:

$$S = \sum_{t=1}^{t_{max}} \sum_{x=1}^{x_{max}} d_x^t, \quad S \leq S_{max}$$

for local dose:

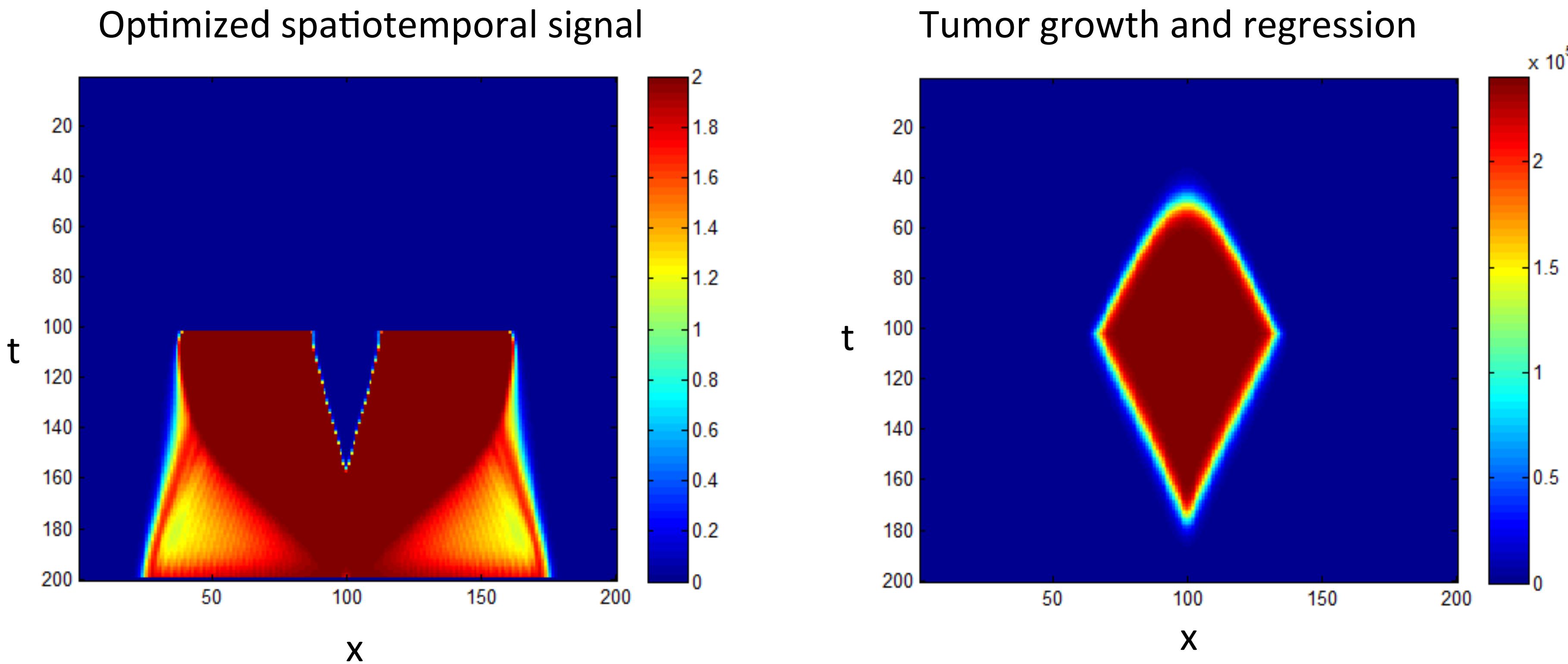
$$d_x^t \leq d_{max}$$

Model simulation (without treatment)



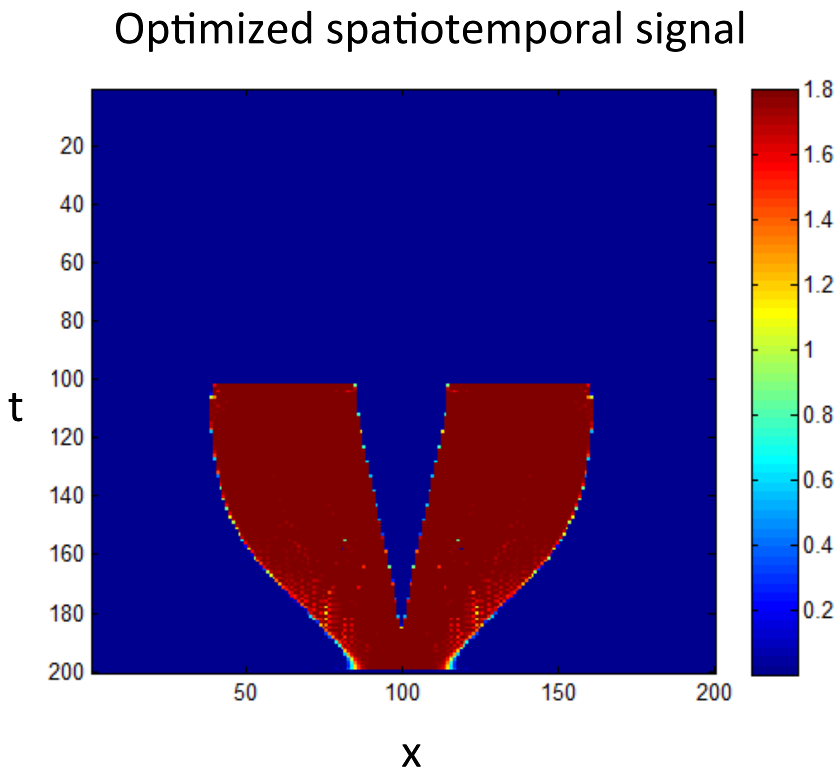
$$D = 18,\ \rho = 35,\ k_t = 2.4\mathrm{e}5$$

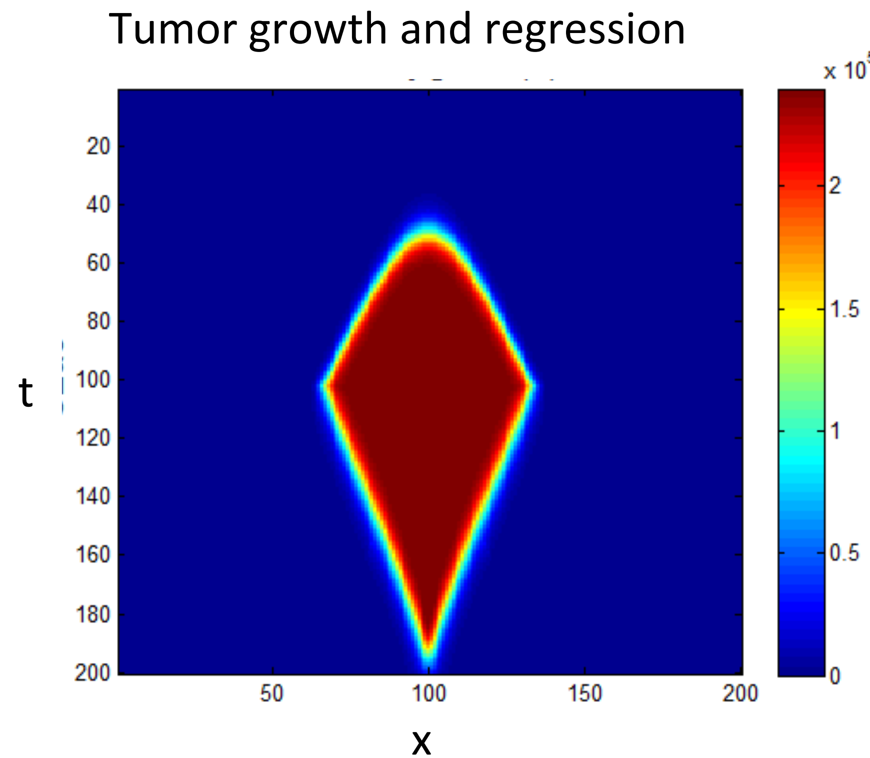
Optimization results of the spatiotemporal irradiation



$$d_{max} = 2$$
$$S_{max} = 2.3e4$$
$$J = 346$$

Optimization results of the spatiotemporal irradiation

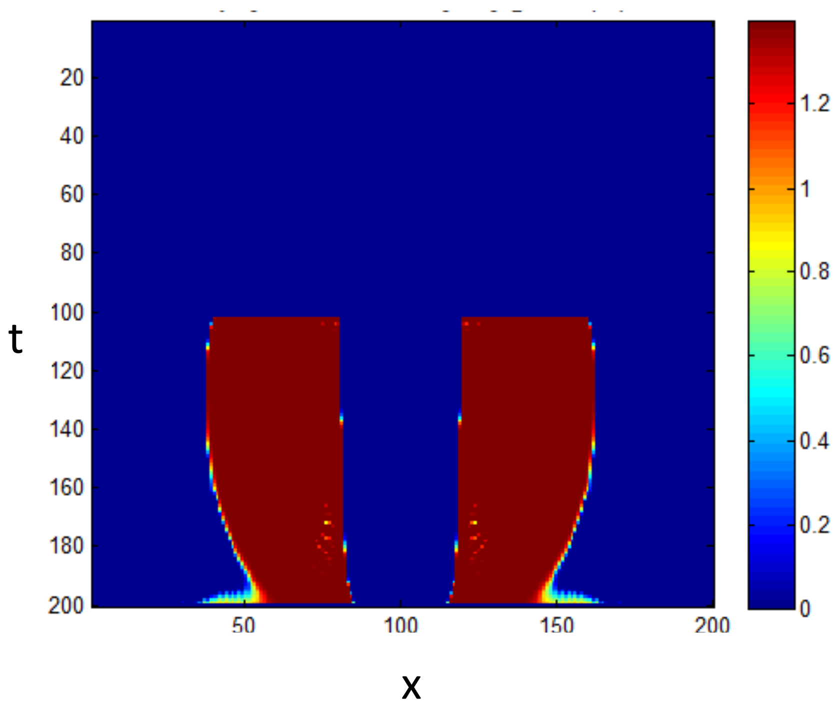




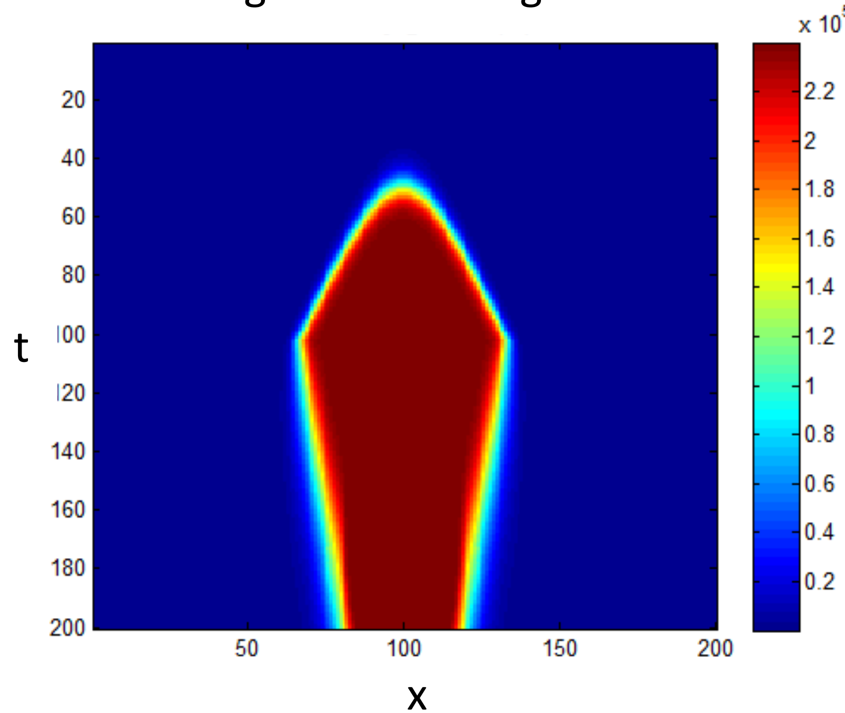
$$d_{max} = 1.8$$
$$S_{max} = 1.4\text{e}4$$
$$J = 2.9\text{e}5$$

Optimization results of the spatiotemporal irradiation

Optimized spatiotemporal signal



Tumor growth and regression



$$d_{max} = 1.4$$
$$S_{max} = 1.1\text{e}4$$
$$J = 9.9\text{e}6$$

Further work

- Different objective function
- Fractioned treatment
- Other models

Further work

- Different objective function
- Fractioned treatment
- Other models

Conclusions

- Effective method for sensitivity analysis w.r.t. spatiotemporal control
- May be used for spatiotemporal control optimization
- Not limited to biological models

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Thank you!