Modeling study of cerebral blood flow redistribution during cortical spreading depression

Tristable fronts and oscillatory vascular responses

Dmitry Postnov

Saratov State University, Russia

Andrey Verisokin and Darja Verveyko

Kursk State University, Russia

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CSD and other spreading depolarization events

Pioneering works
Leao, A.A.P., 1944. J. Neurophysio .
Grafstein, B., 1956. J. Neurophysiol.

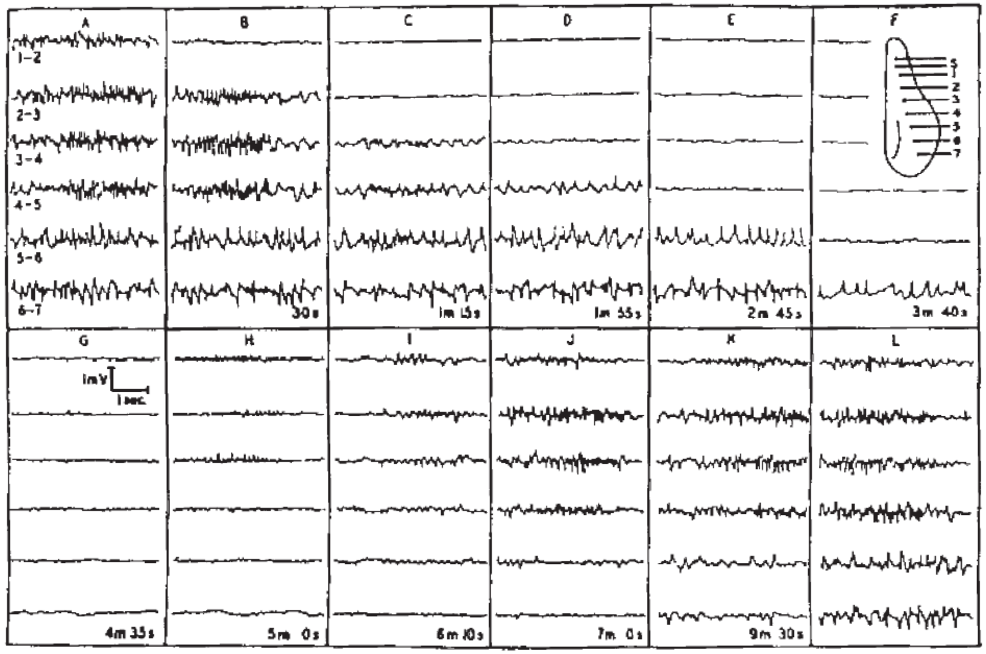
Discussion of mechanisms
Somjen, G. G. Physiol. Rev. (2001).
Miura, Huang, Wylie, 2007.
Eur. Phys. J. Spec.Top.

Spreading depolarization in retina
Dahlem et al., 2010. Physica D 239

Clinical relevance:
Lauritzen et al J. Cereb. Blood Flow Metab. (2011).

Cortical spreading depression and migraine
Nature Reviews Neurology 9, 637-644 (November 2013)
Andrew C. Charles, Serapio M. Baca

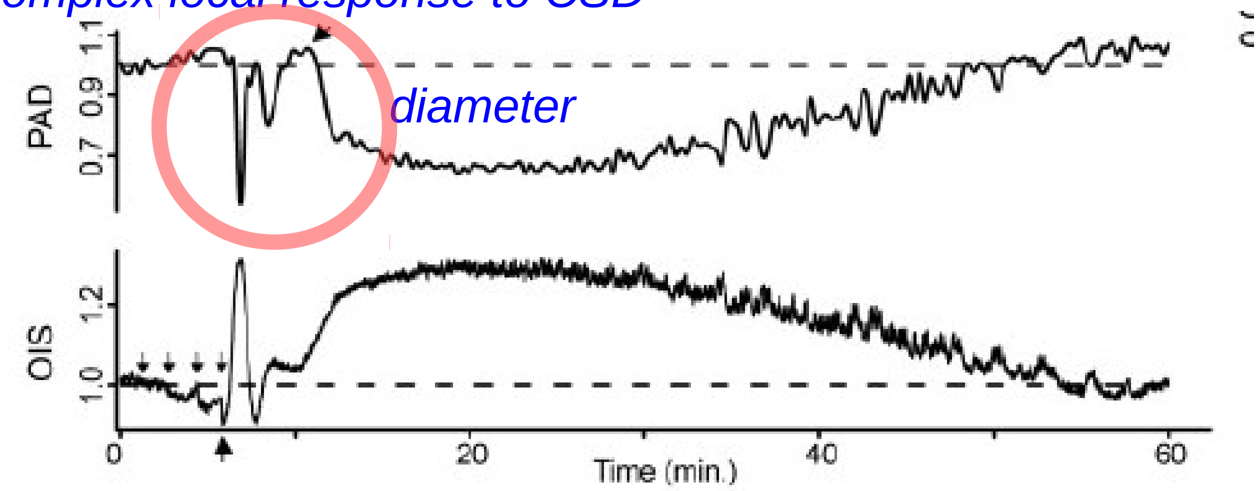
Recent review on topic
Pietrobon & Moskowitz, Nature Reviews Neuroscience (2014)



Original drawing of CSD by A. Leao

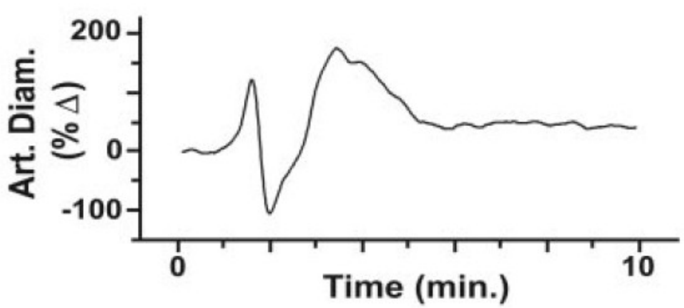
Spreading depolarization (SD) and cerebral blood flow (CBF)

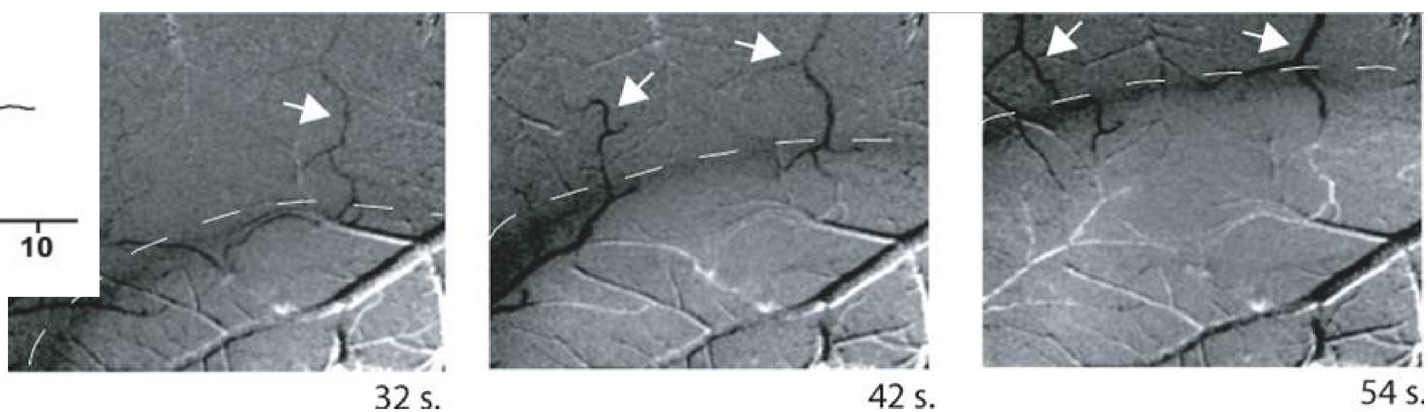
Complex local response to CSD



Chang et al., Brain (2010)

Arterioles show the dilation ahead of CSD front





Brennan et al. J Neurophysiol, (2007).

Modeling studies on topic

Grafstein In: Brazier, M.A.B. (Ed.), Brain Function. Cortical Excitability and Steady Potentials, (1963)

Kager, Wadman, Somjen, J. Neurophysiol. (2002).

Bennett et al. Biophys. J., (2008),

Chapuisat et al., Progress Biophys Mol. Biol. (2008),

Chapuisat et al., ESAIM: Proc. (2007).

Dahlem and Chronicle, Prog. Neurobiol.(2005).

Dahlem et al., Physica D (2010)

Postnov et al., Brain Research, (2012)

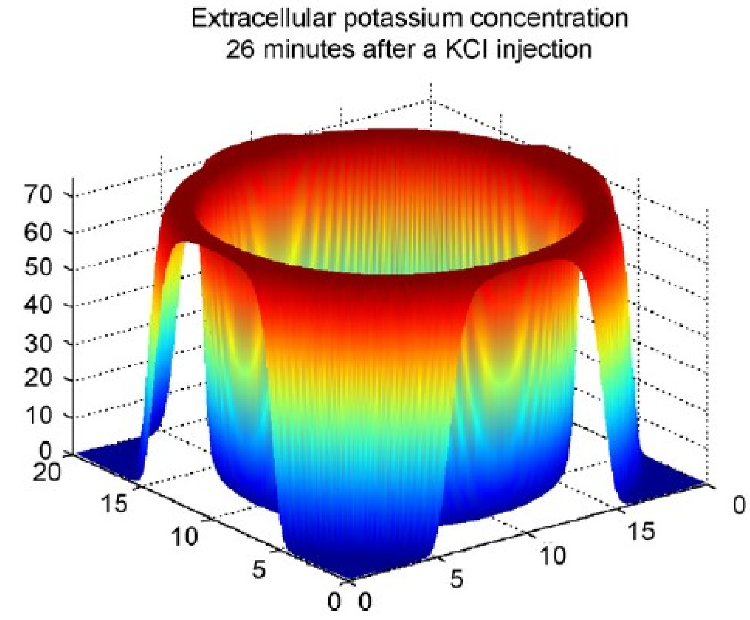


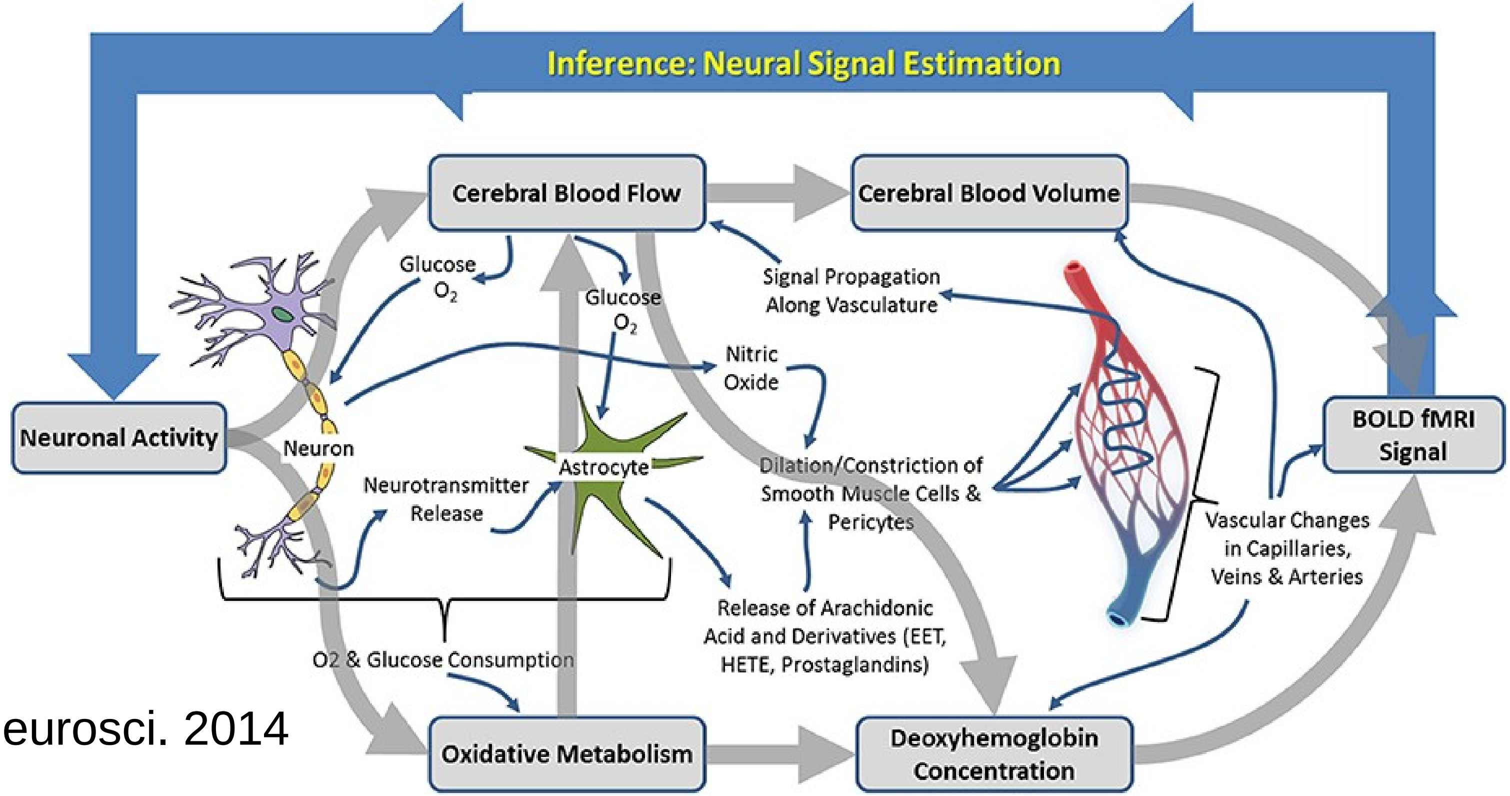
Figure from: Chapuisat et al., 2007

The objective of our study is to provide the reasonably simple but still physiologically-tractable computational model that would capture the main pathways that govern the reciprocal coupling between the neuronal activity and CBF.

fMRI issue:

" interpretation of BOLD fMRI studies of individuals with different ages or pathology might be more challenging than is commonly acknowledged."

Esposito, Deouell & Gazzaley, Nature Reviews Neuroscience (2003)



Martin C. , Front Neurosci. 2014

Starting point: 4D model of CSD

D. E. Postnov, F. Müller, R. B. Schuppner, and L. Schimansky-Geier, Phys. Rev. E, 2009
D.E. Postnov, D.D. Postnov, L. Schimansky-Geier, Brain Research, 2012

NOISE

Modified FitzHugh-Nagumo model

$$\varepsilon_v \, \dot{v} = v - v^3/3 - w + z - \mu_u u^n (v+1)^3 + C(x,y,t),$$

$$\tau(v)\, \dot{w} = A + Bv - w + \mu_u u^n,$$

I

Second activator (extracellular potassium)

$$\varepsilon_z \, \dot{z} = \alpha_z \Psi(v) - z + \gamma \left(\frac{\partial^2 z}{\partial x^2} + \frac{\partial^2 z}{\partial y^2} \right),$$

II

Second inhibitor (slow metabolic losses)

$$\varepsilon_u \, \dot{u} = \alpha_u \Psi(v) - u,$$

III

Sigmoid function to detect spikes

$$\Psi(v) = \frac{1}{2}\left(1 + \tanh\left(\frac{v}{v_s}\right)\right),$$

Time scales for spike and Recovery are different

$$\tau(v) = \tau_l + (\tau_r - \tau_l)\Psi(v).$$

Potassium in extracellular space

$$\varepsilon_z \partial_t z = \alpha_z \psi(v) - (1 + k_z(p - p_v)\rho_0 r^4)z + \gamma\left(\partial^2_{xx} z + \partial^2_{yy} z\right)$$

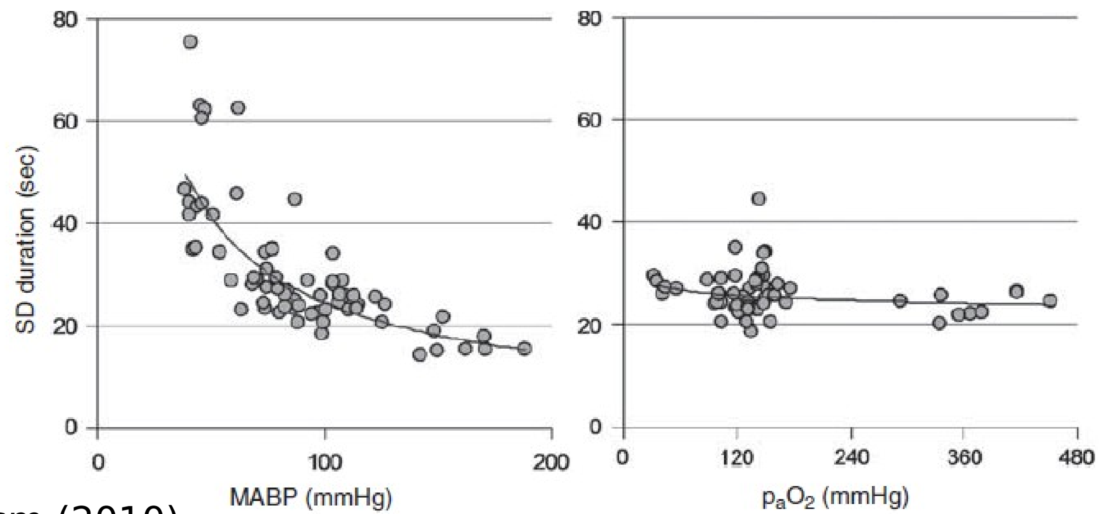
Flow ~ perfusion

Diffusion

$$\psi(v) = \frac{1}{2}\left(1 + \tanh\left(\frac{v}{v_s}\right)\right),$$

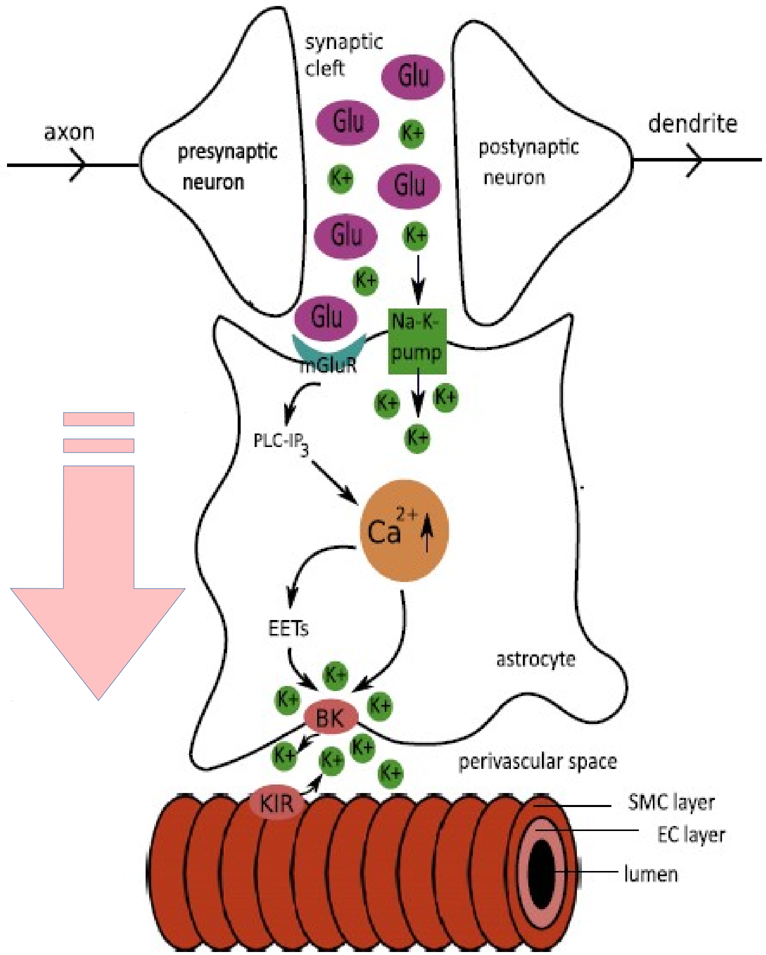
Comes from neuronal part of model

SD duration is controlled by the perfusion rate,
rather then by oxigenation!



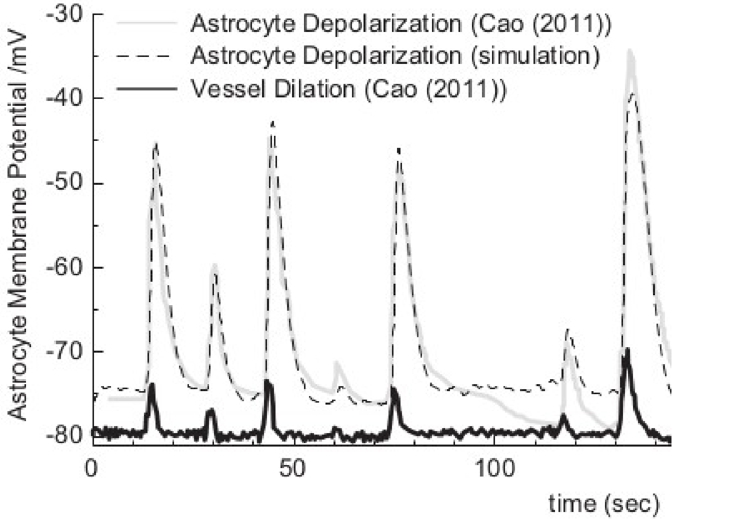
Sukhotinsky et al,
Journal of Cerebral Blood Flow & Metabolism (2010)

Neurovascular coupling

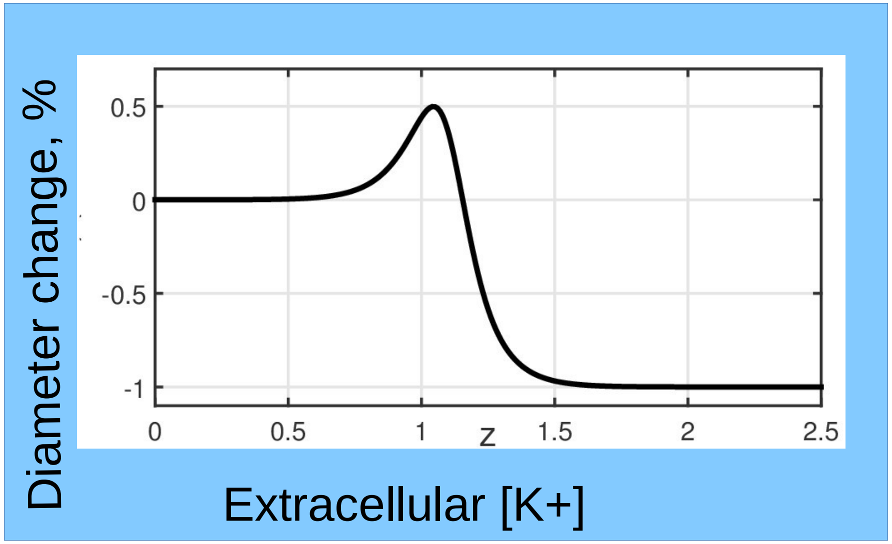


Farr, David, J of Theoretical Biology (2011)

Why we drop astrocytes from our model



Witthoft, Karniadakis, Journal of theoretical biology, 2012

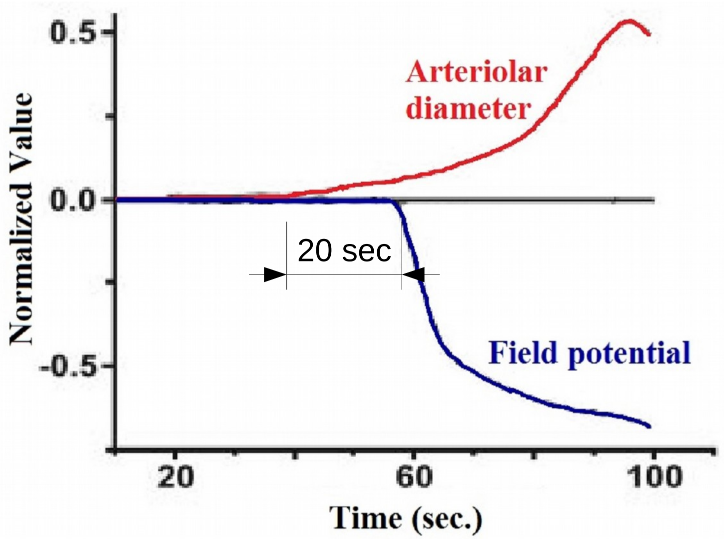


Spatial coupling: functional hyperemia + conducted vasodilation

Gustafsson, Nolstein-Rathlou,
Acta Physiol Scand (1999)

Bagher, Segal, Acta Physiol (2011)

Hill, Microcirculation (2012)

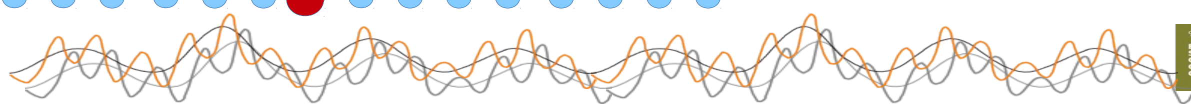


Brennan et al. J Neurophysiol, (2007).

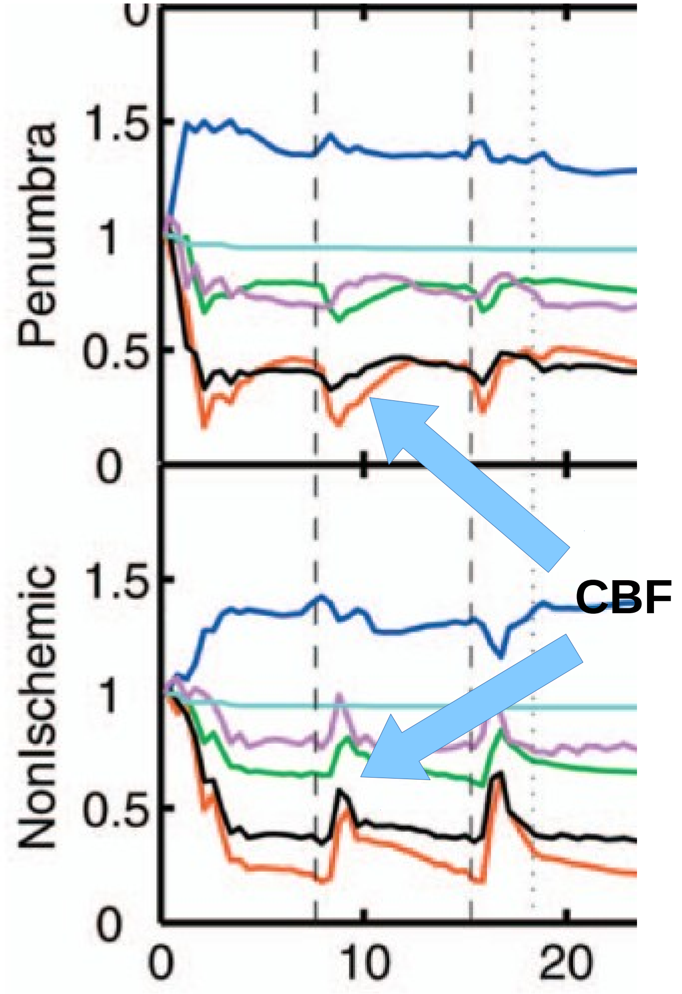
Sum over area defined by

window function

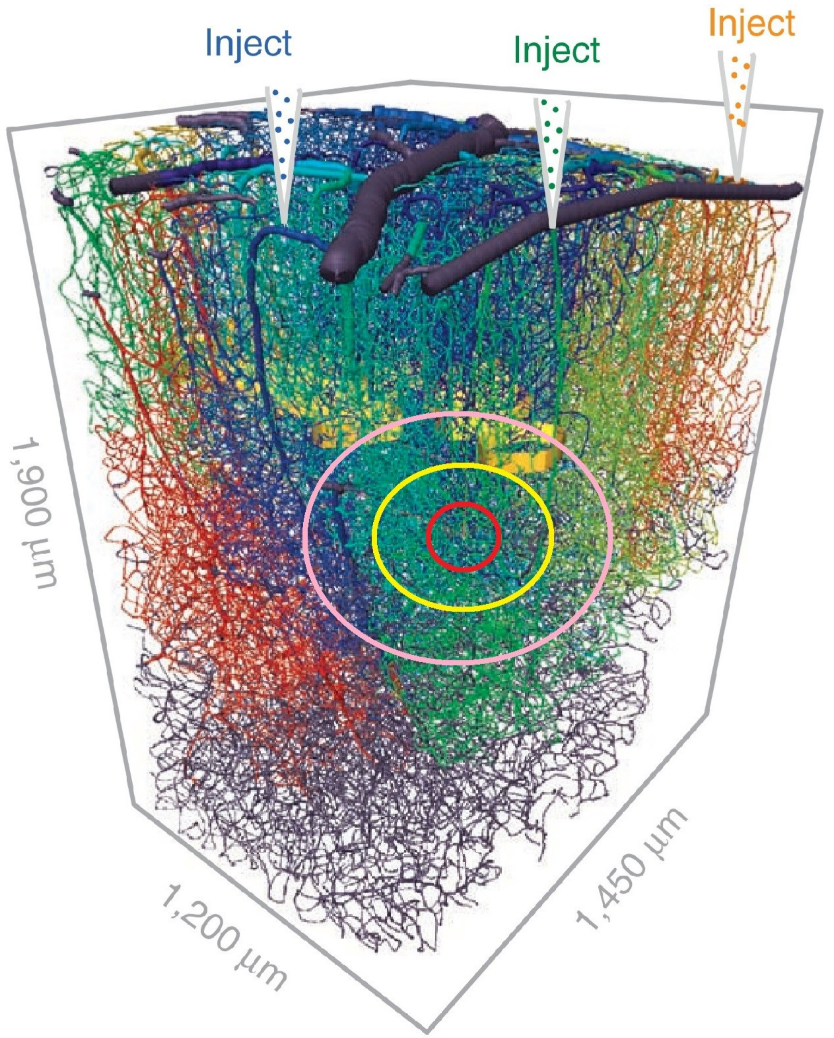
$$\varepsilon_r \partial_t r = \sum_{x,y} (W R_{x_0,y_0} p(z(x,y))) - r(x_0, y_0),$$



Spatial coupling: flow sharing

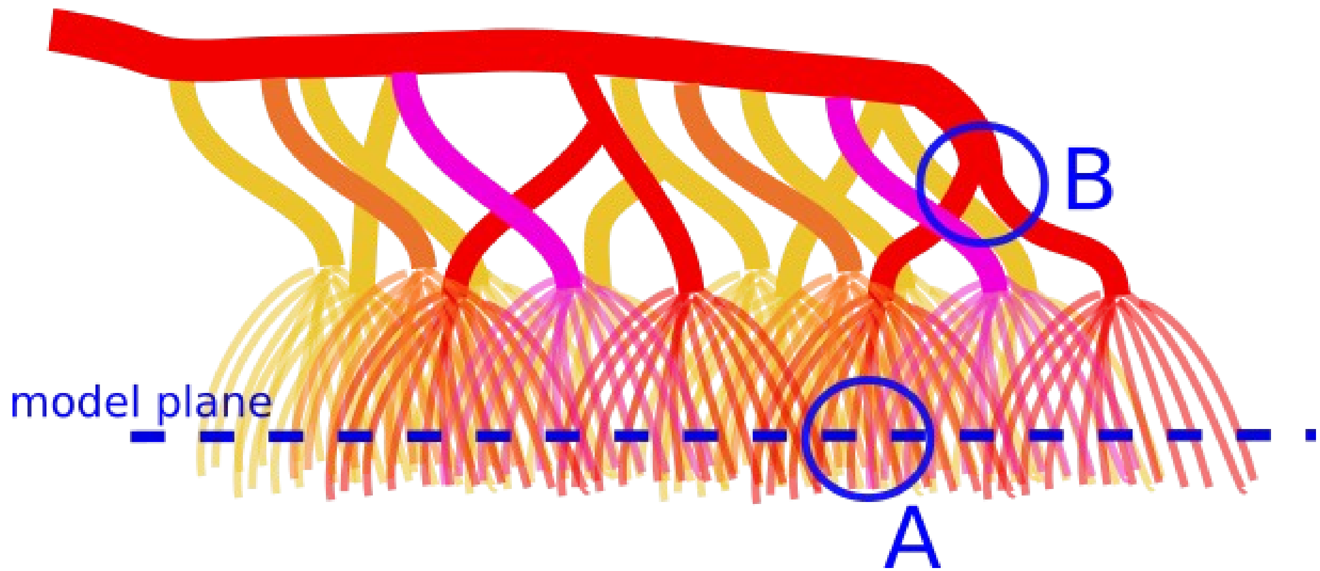


Jones et al. J Biomed Opt. 2008,



Blinder et al., 2013, Nature Neuroscience

Spatial coupling: flow sharing



$$\varepsilon_p \partial_t p = 1 - p - (p - p_v)\rho_0 \sum_{x,y} (W P_{x_0,y_0} r^4(x,y)),$$

Upstream shared flow

Inverse total resistance of one “ambrella”

Model overview – equations

Model neuron

$$\varepsilon_v \partial_t v = v - v^3/3 - w + z - \mu_n (1-u)^n (v+1)^3 + C(x_0, y_0, t),$$

$$\varepsilon_w(v) \partial_t w = A + Bv - w + \mu_n (1-u)^n + I_{app},$$

Potassium in extracellular space

$$\varepsilon_z \partial_t z = \alpha_z \psi(v) - (1 + k_z (p - p_v) \rho_0 r^4) z + \gamma \left(\partial^2_{xx} z + \partial^2_{yy} z \right)$$

Vessel radius

$$\varepsilon_r \partial_t r = \sum_{x,y} (W R_{x_0, y_0} p(z(x,y))) - r(x_0, y_0),$$

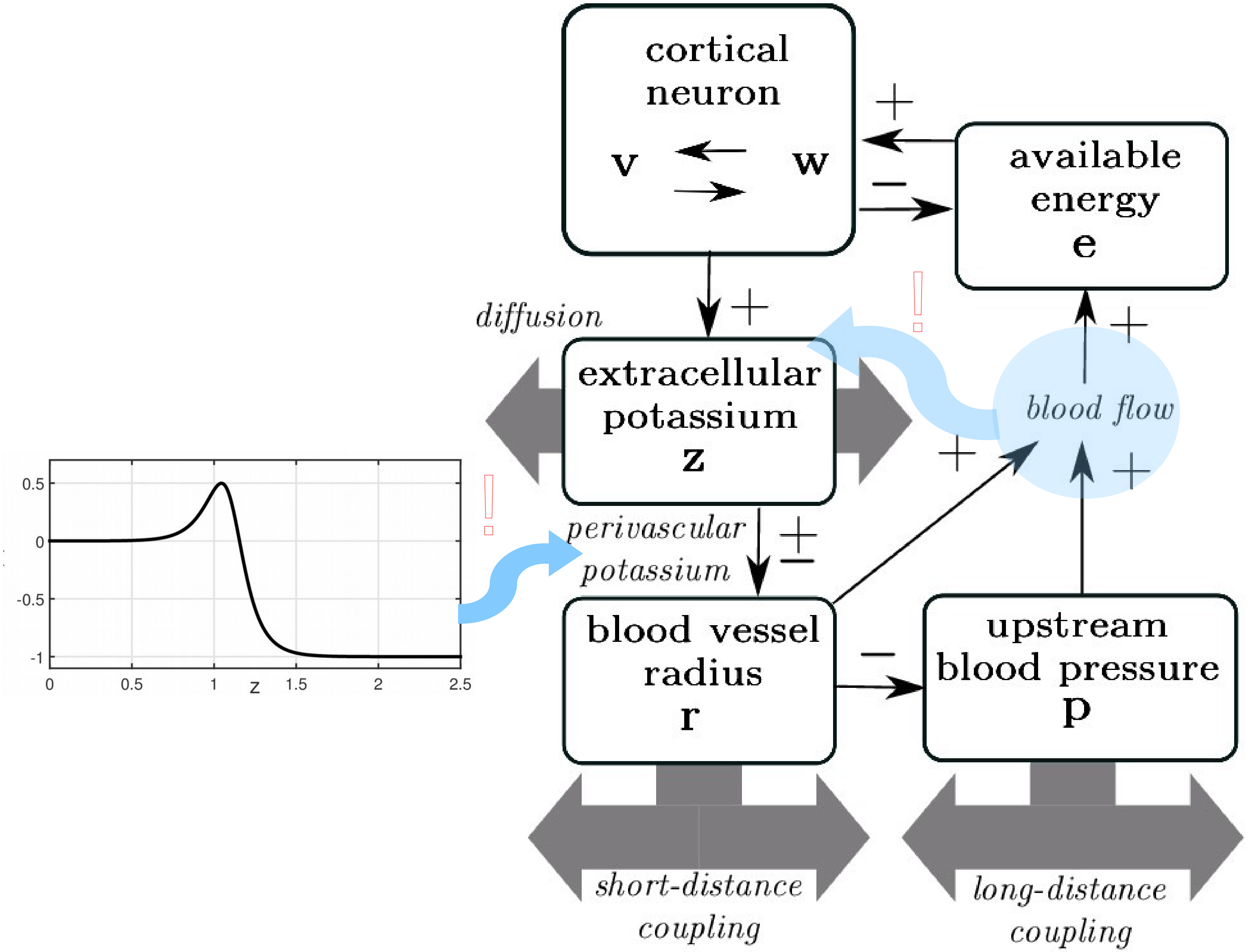
Upstream pressure

$$\varepsilon_p \partial_t p = 1 - p - (p - p_v) \rho_0 \sum_{x,y} (W P_{x_0, y_0} r^4 (x,y)),$$

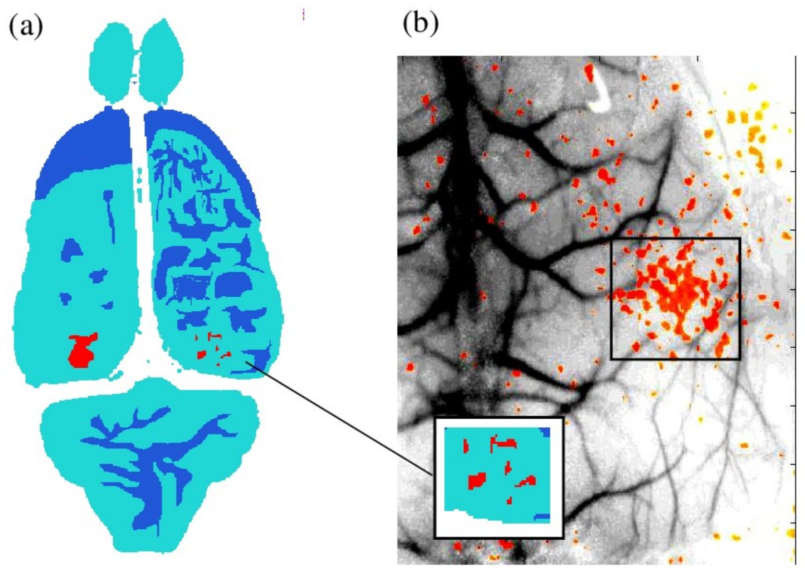
Balance of energy

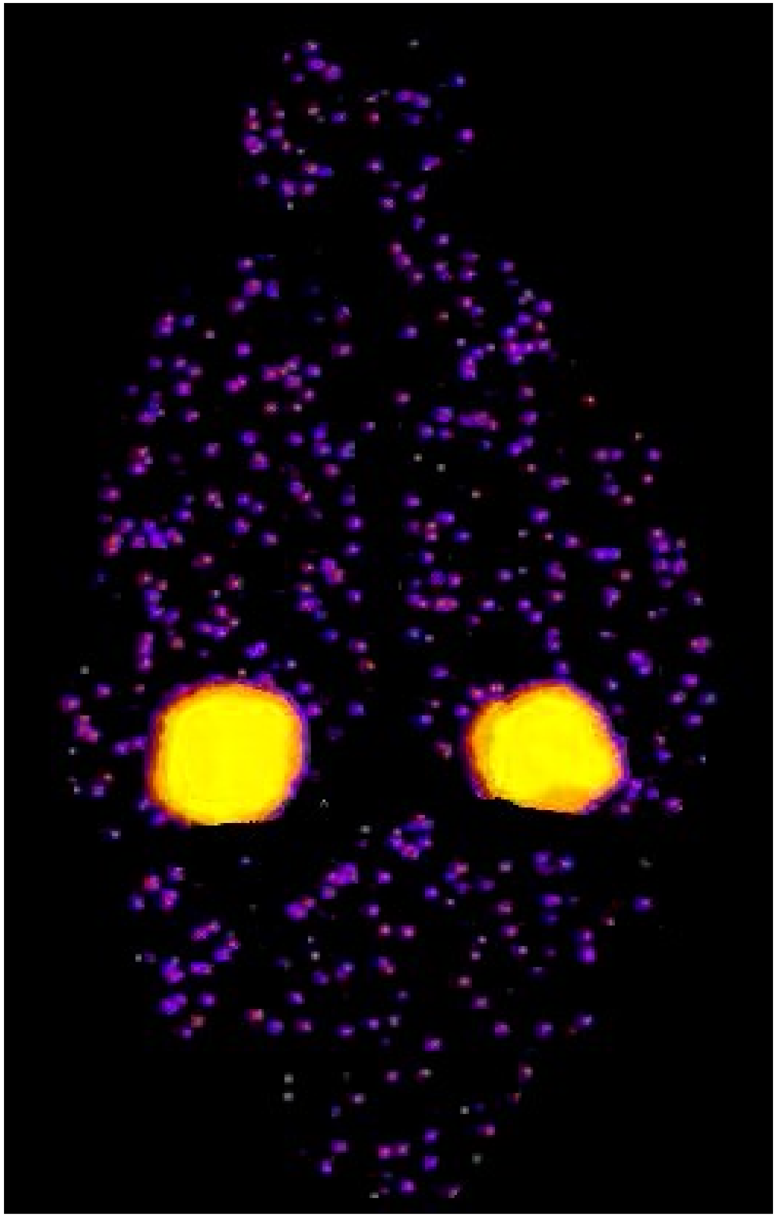
$$\varepsilon_u \partial_t u = (1-u)(p - p_v) \rho_0 r^4 - \beta_u \psi(v),$$

Model overview - pathways



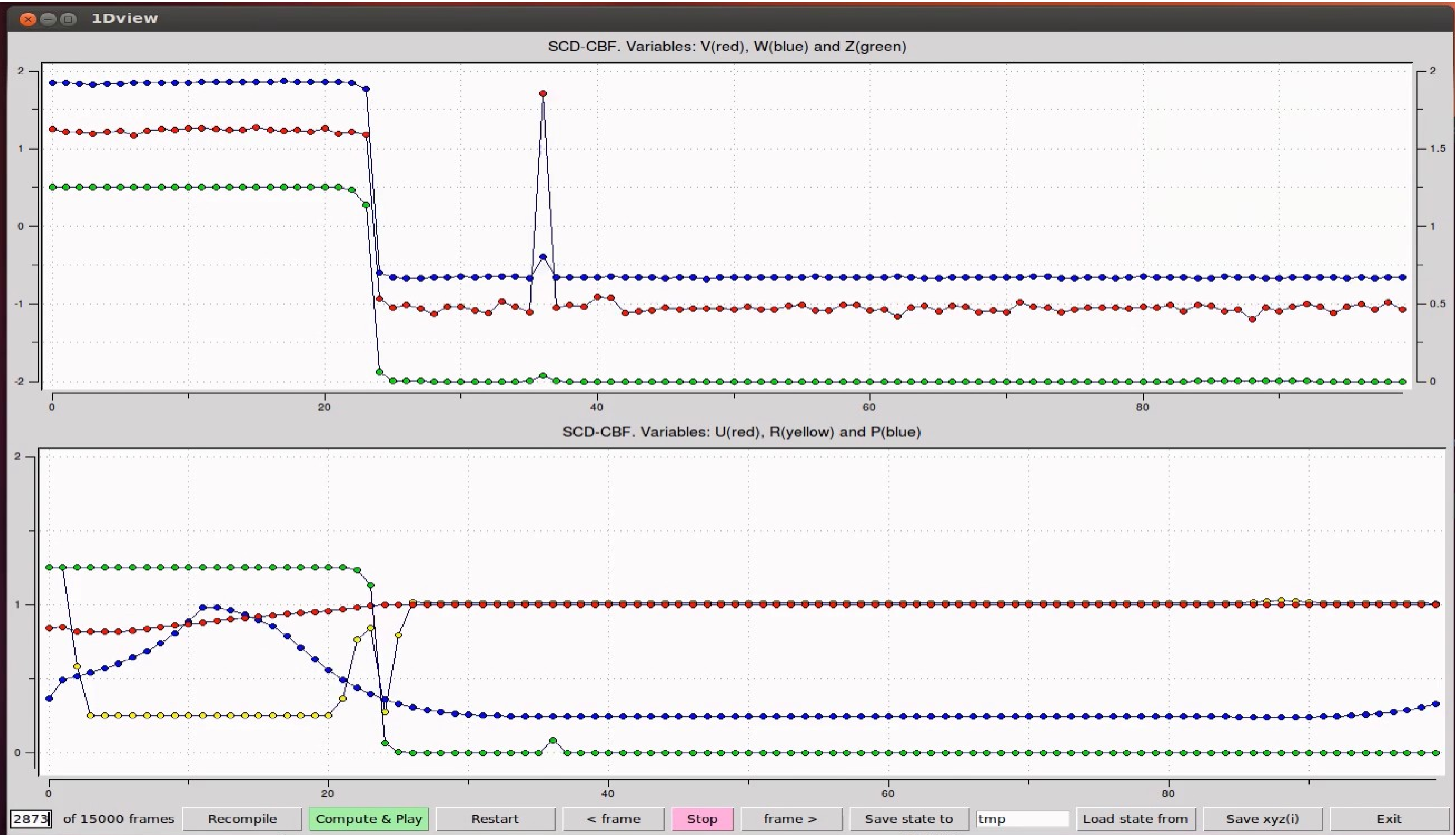
Results: full-scale simulations





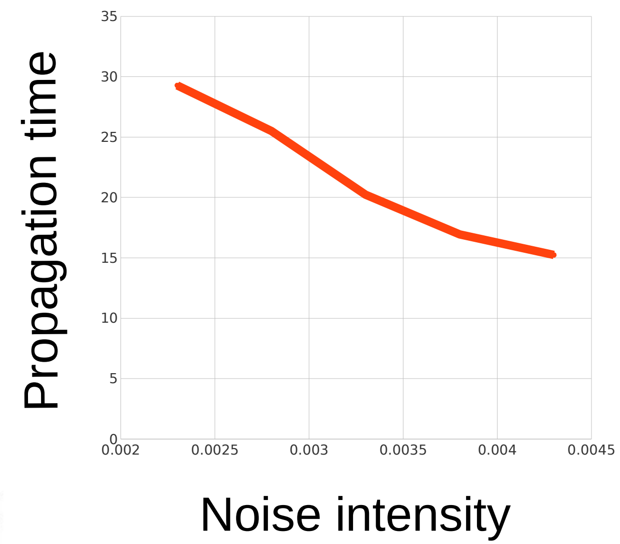
- **Dynamical mechanism of slow propagation of CSD front ? Role of noise?**
- **Rate of perivascular potassium delivery?**
- **Perfusion impact on vascular response?**

Results : CSD front in motion

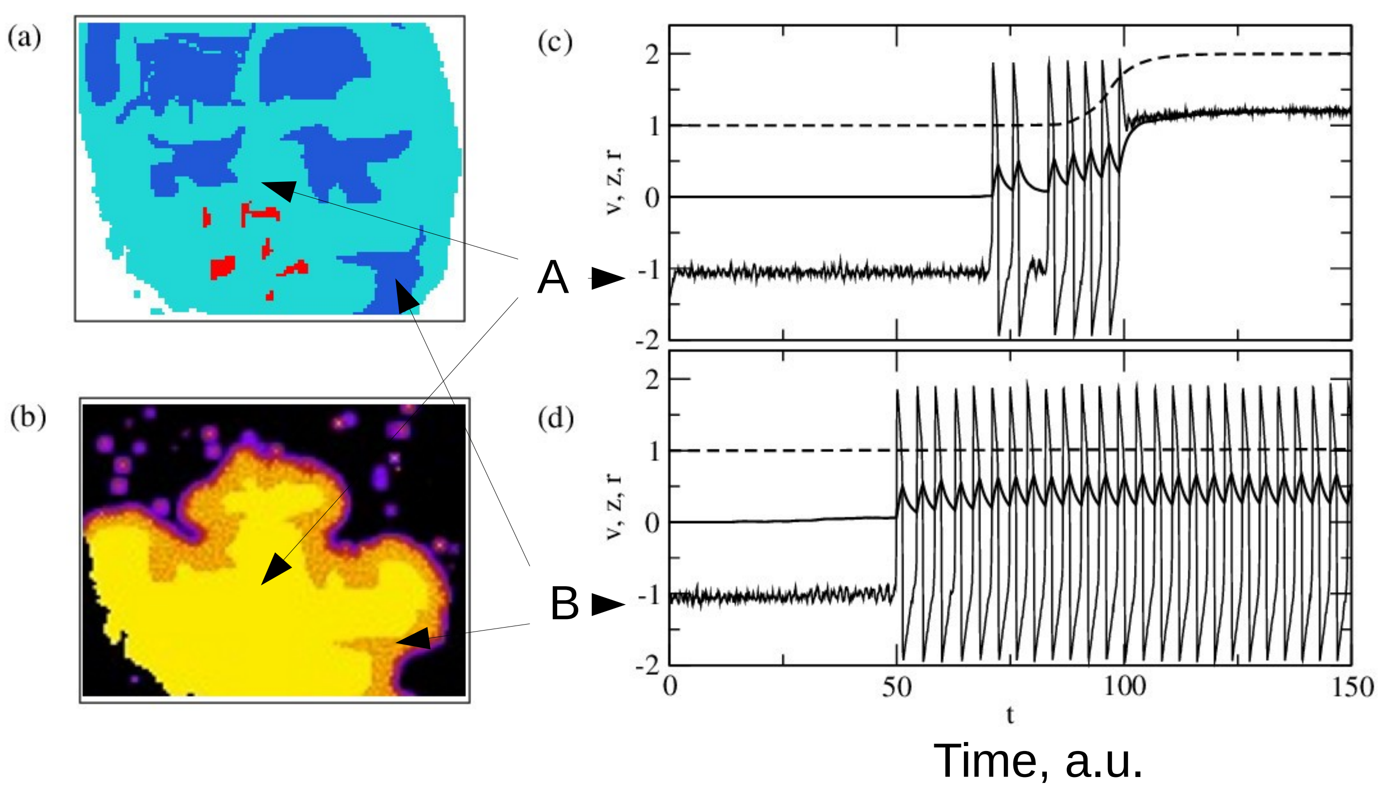


Results: front propagation

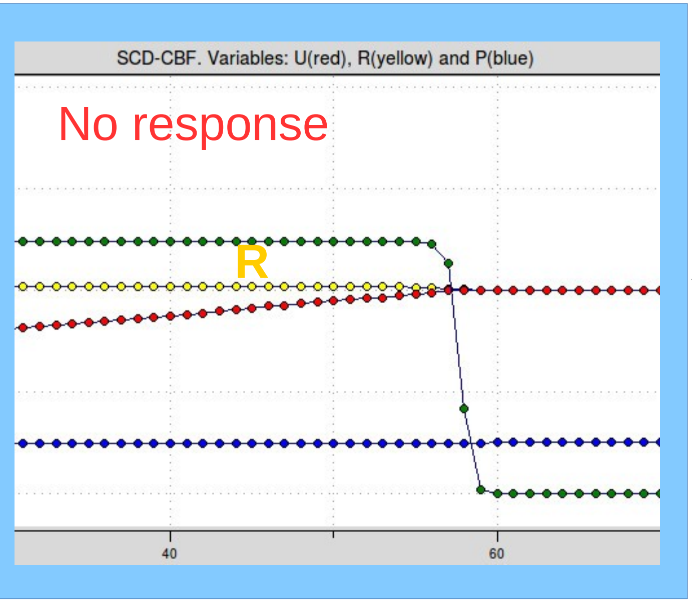
Noise speeds up the CSD front

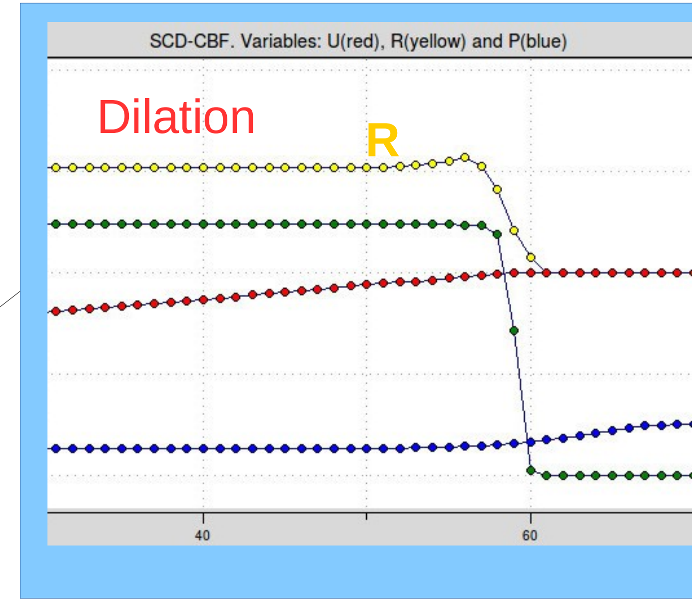


Oscillatory state facilitated by high perfusion

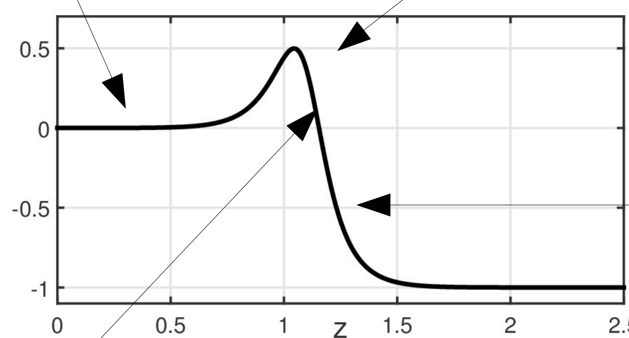


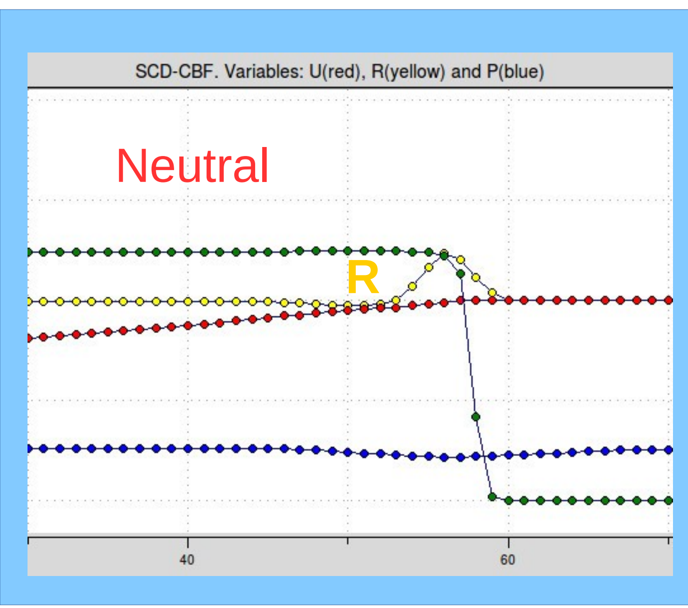
Results: different rate of perivascular potassium delivery evokes different vascular response patterns

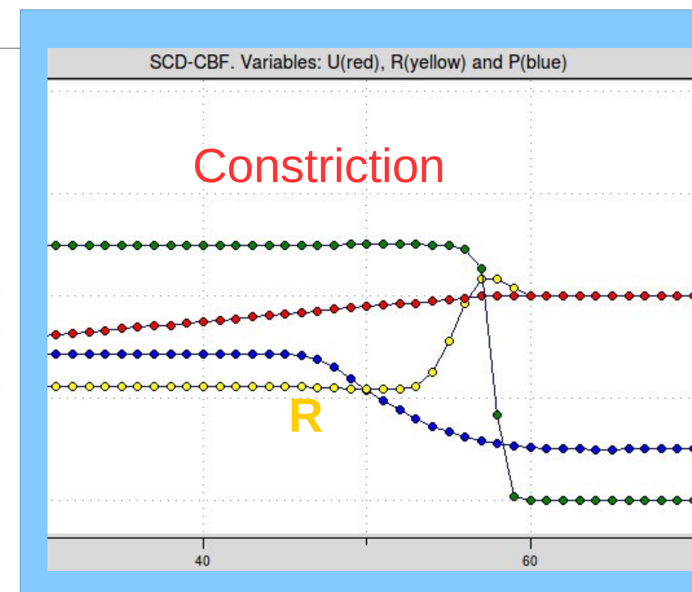


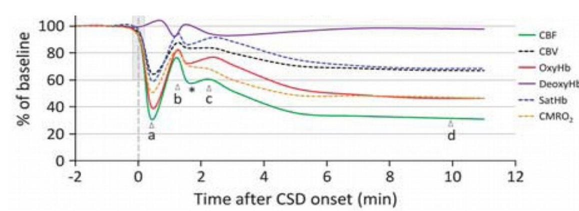


The relative change of R vs Z









Yuzawa et al., Jof Cerebral Blood Flow & Metabolism (2011)

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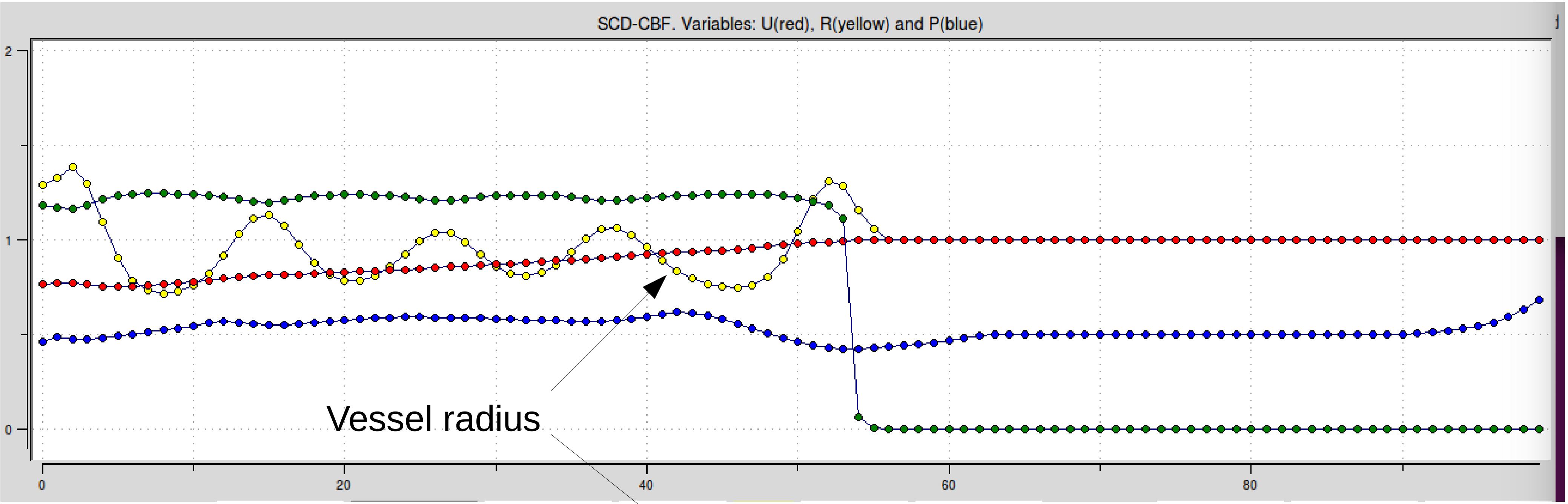
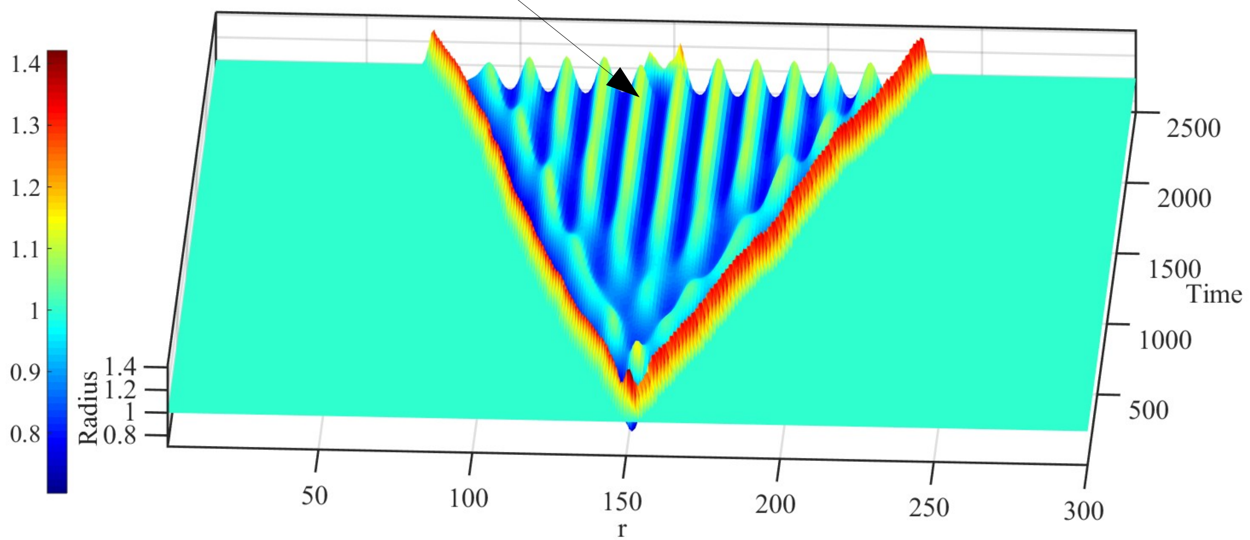
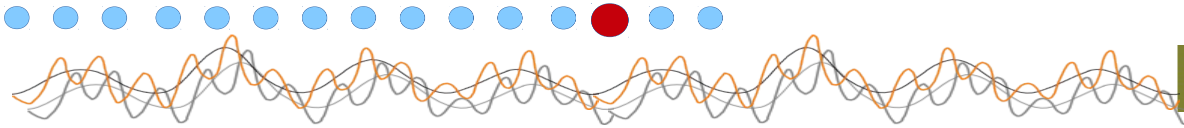
Results: Perfusion feedback evokes the **standing vascular patterns**







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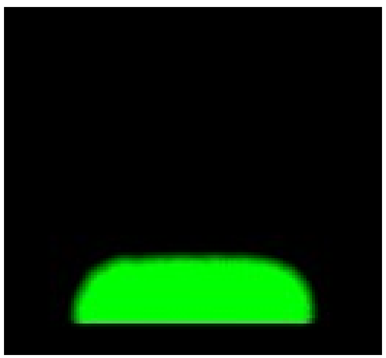
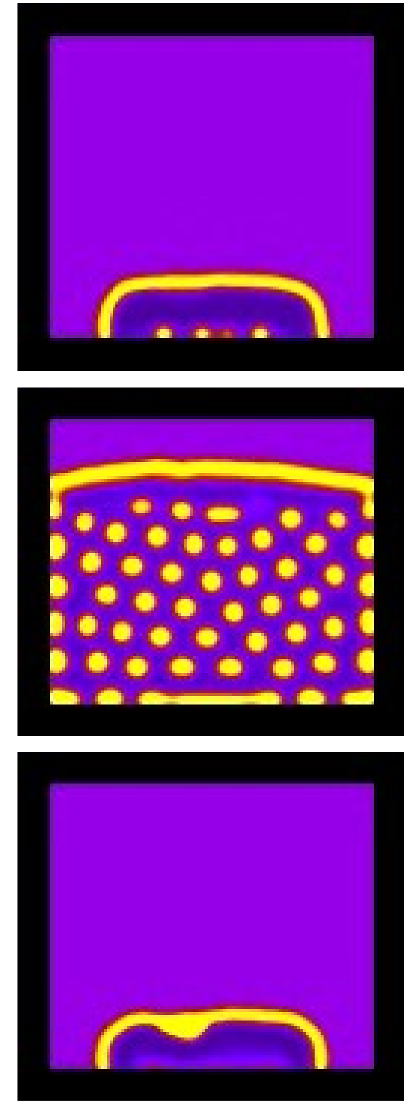
Results: Standing vascular patterns in 2D

Extracellular potassium spreads
Over available space





Perfusion-mediated feedback
forms the spatial patterns
of vessel radius that persists
until the depolarization gone
(shown at three different parameter sets)

Conclusions

With proposed model, the obtained results are in agreement with known physiological facts about spreading depression, including the main functional states of cortex during the CSD.

Predicted types of vascular response are in qualitative agreement with experimental results.

The propagated front of persistent depolarization normally contains the transient phase of intensive neuronal oscillations. This oscillatory state becomes the “third player” of CSD scenario.

Under the variation of perfusion rate the model shows *the tendency* to formation of **standing patterns of vascular responces**. It might be the important mechanism that mediates the other perfusion-dependent processes, including the the lifetime of depolarized state and the metabolic recovery rate.

Many thanks to collaborators,

Andrey Verisokin

Darja Verveyko

Kursk State University, Russia

Some publications on topic

A Verisokin, D. Verveyko , and D. E. Postnov
Computational model of cerebral blood flow redistribution during cortical spreading depression
Proc.of SPIE, in press (2016)

D.E. Postnov, D.D. Postnov, L. Schimansky-Geier.
Self-terminating wave patterns and self-organized pacemakers in a phenomenological model of spreading depression. Brain Research, 2012. Vol.1434, p.200-211.

D D Postnov, D E Postnov, D J Marsh, N-H Holstein-Rathlou, O V Sosnovtseva.
Dynamics of Nephron-Vascular Network.
Bulletin of Mathematical Biology. 10/2012

D.E. Postnov, A.P. Chetverikov, D.D. Postnov.
Stimulus-induced response patterns of medium-embedded neurons.
Eur. Phys.J. 2010, Special Topics 187, p.241-253.

Thank you for attention!

13/04/2016