Комбинированное влияние уровня поступления питательных веществ и механических свойств тканей на рост доброкачественной опухоли

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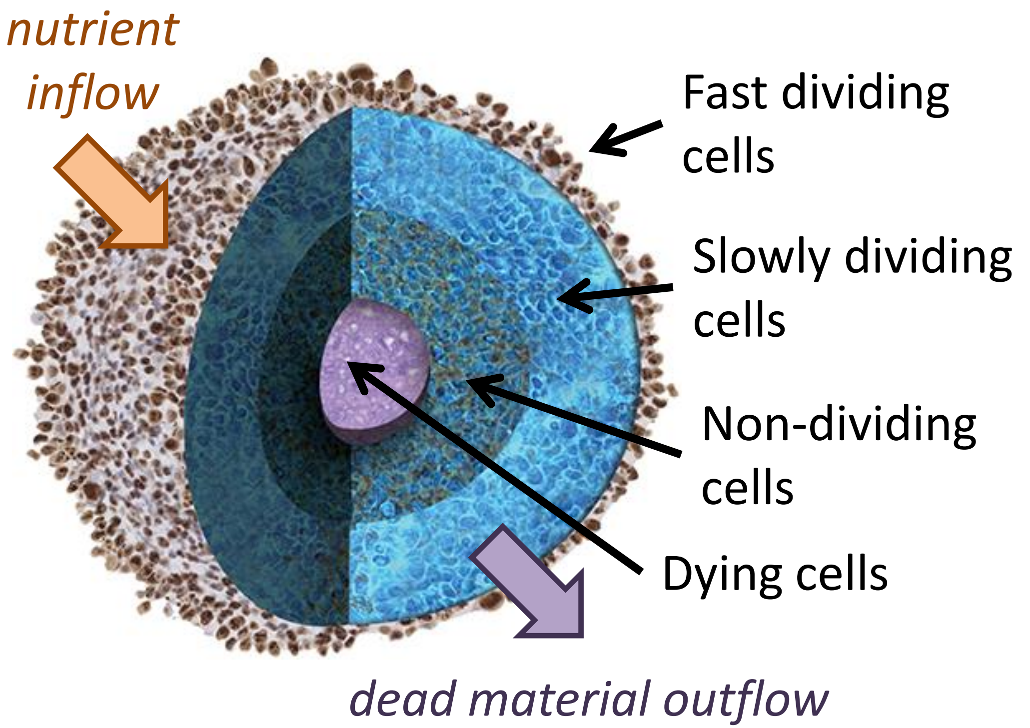
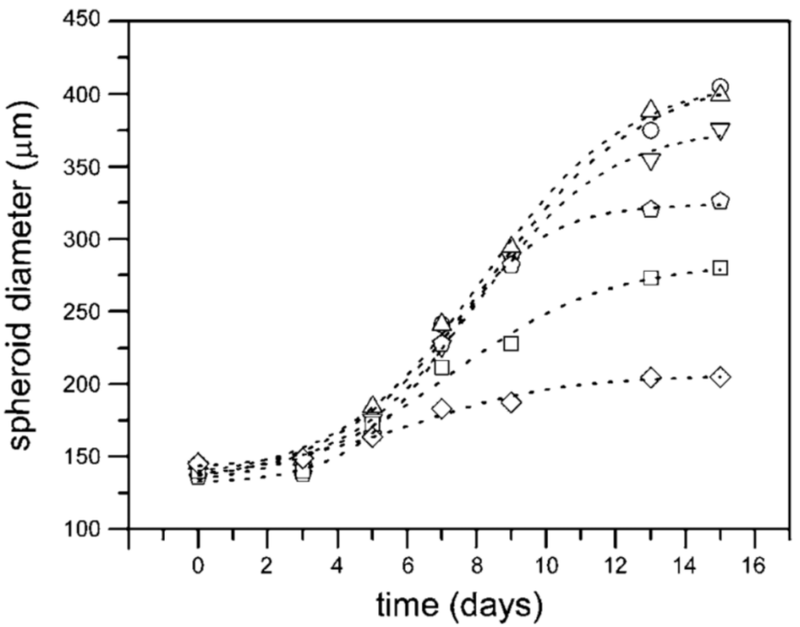
«Математические модели и численные методы в биологии и медицине»
2-3 ноября 2021

Growth-limiting factor #1: diffusional limitation of nutrient supply

Tumor spheroid – 3D model of tumor in vitro



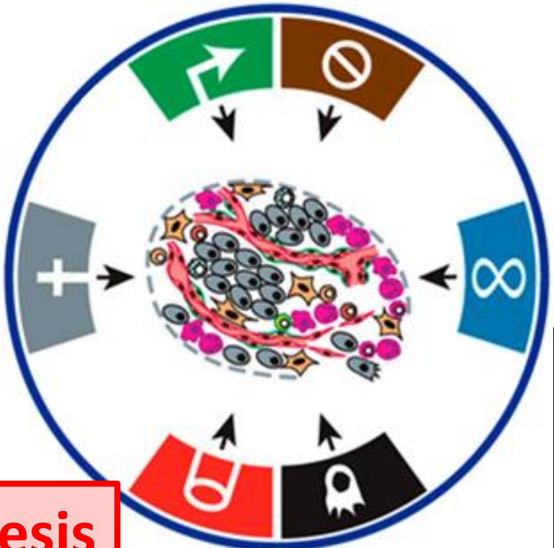
Experimental growth curves



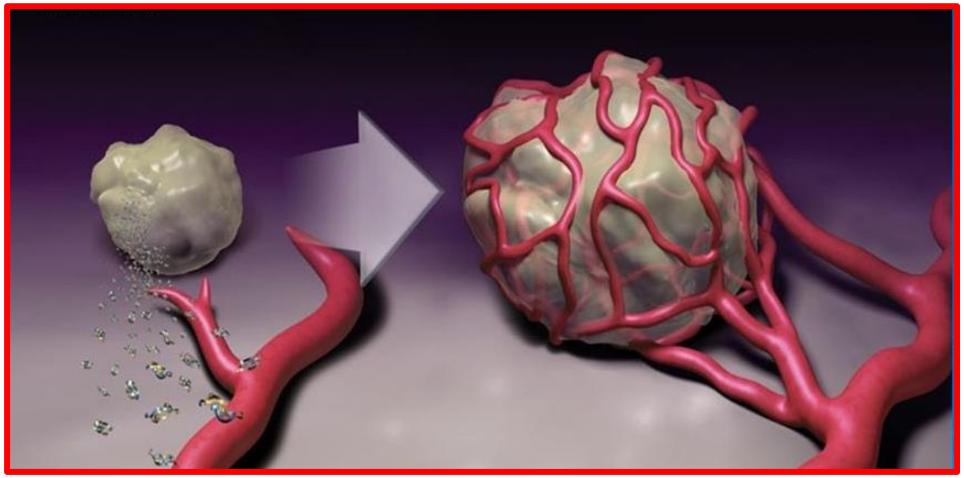
Horman S. R. //Special Topics in Drug Discovery. – 2016. – p. 73.

Hardelauf H. et al. //Lab on a Chip. – 2011. – Vol. 11. – №. 3. – pp. 419-428.

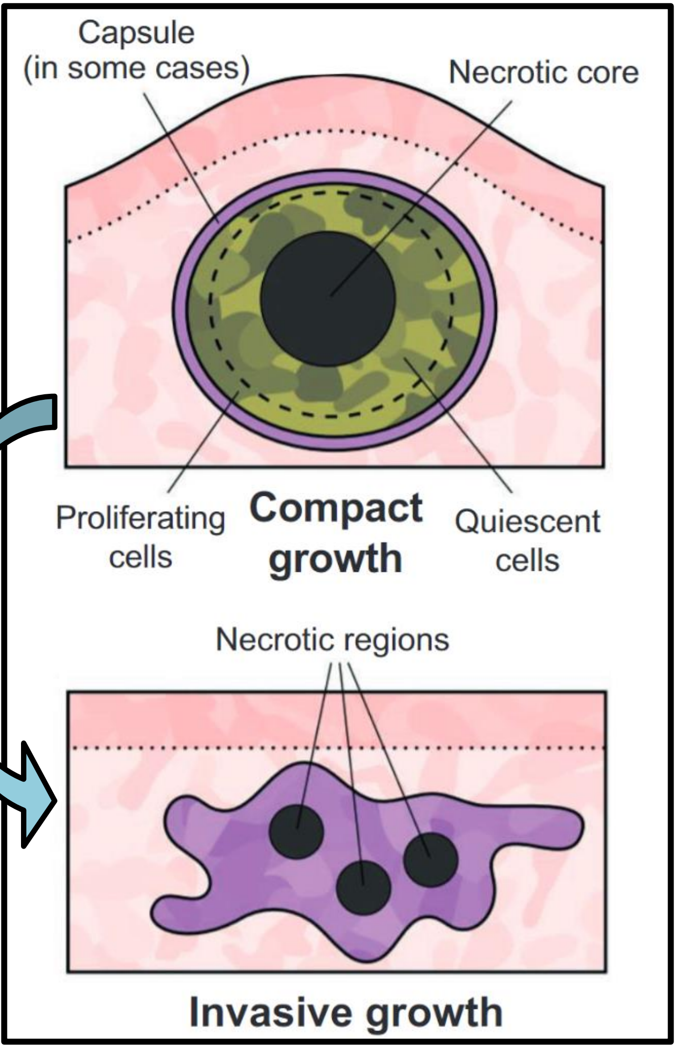
Mechanisms to overcome starvation



Angiogenesis



Invasion of nearby tissues

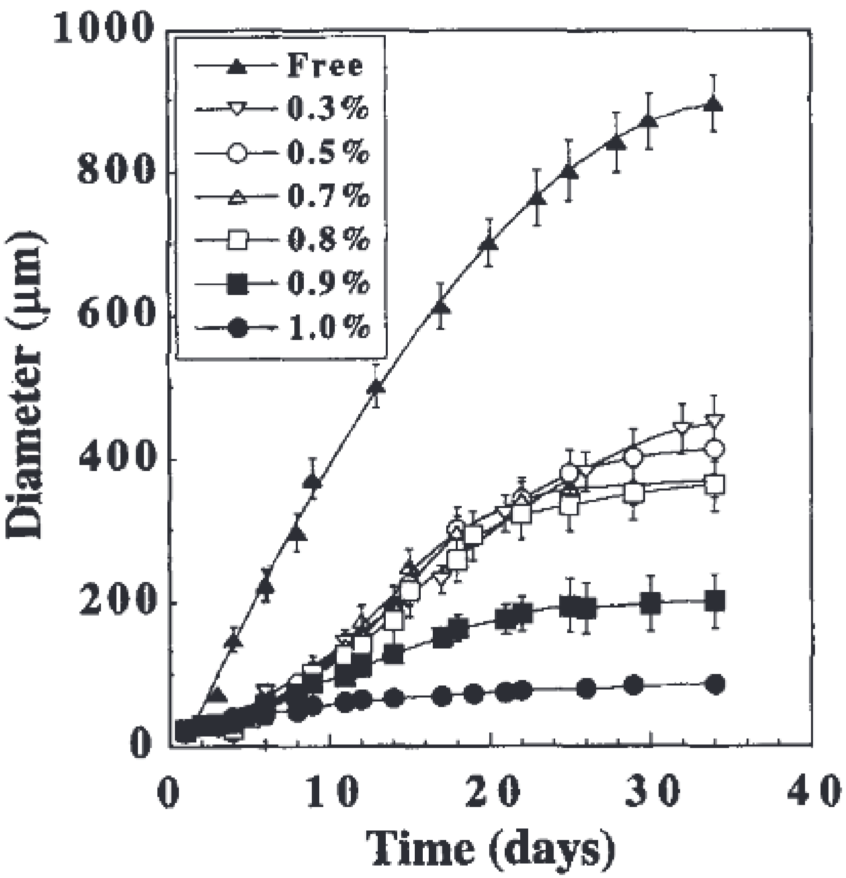


Bergers, G., & Benjamin, L. E.
Nature reviews cancer, *3*(6), 401-410. (2003)

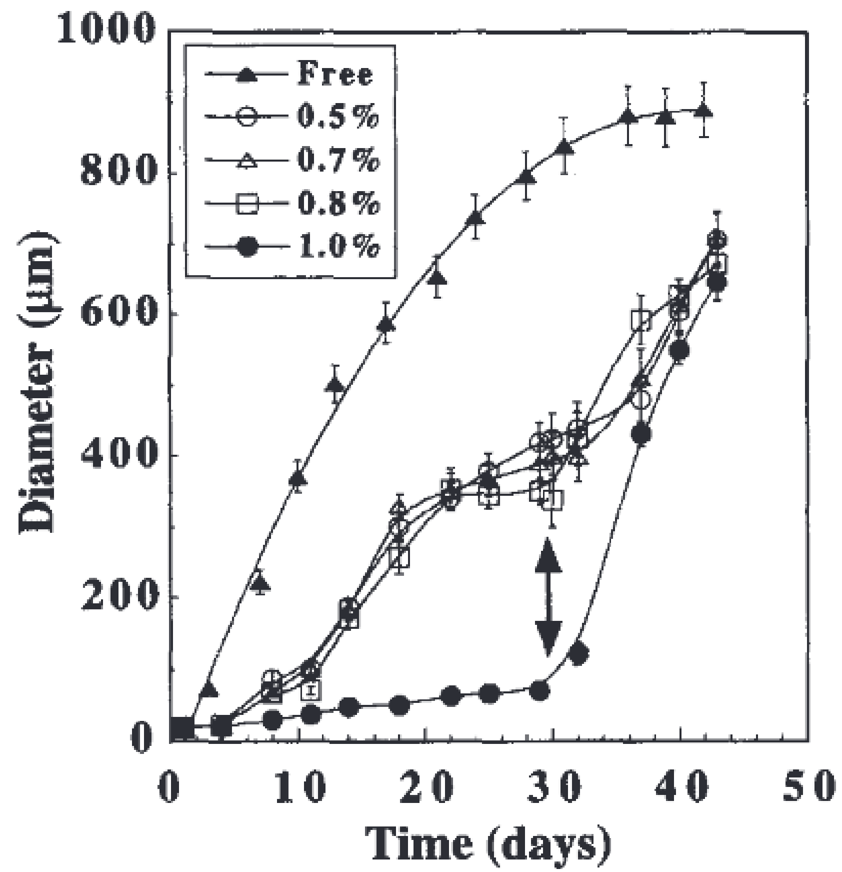
Vassilevski Y. et al. Personalized Computational Hemodynamics. – Academic Press, 2020.

Growth-limiting factor #2: stress-induced growth inhibition

Constant agarose concentration

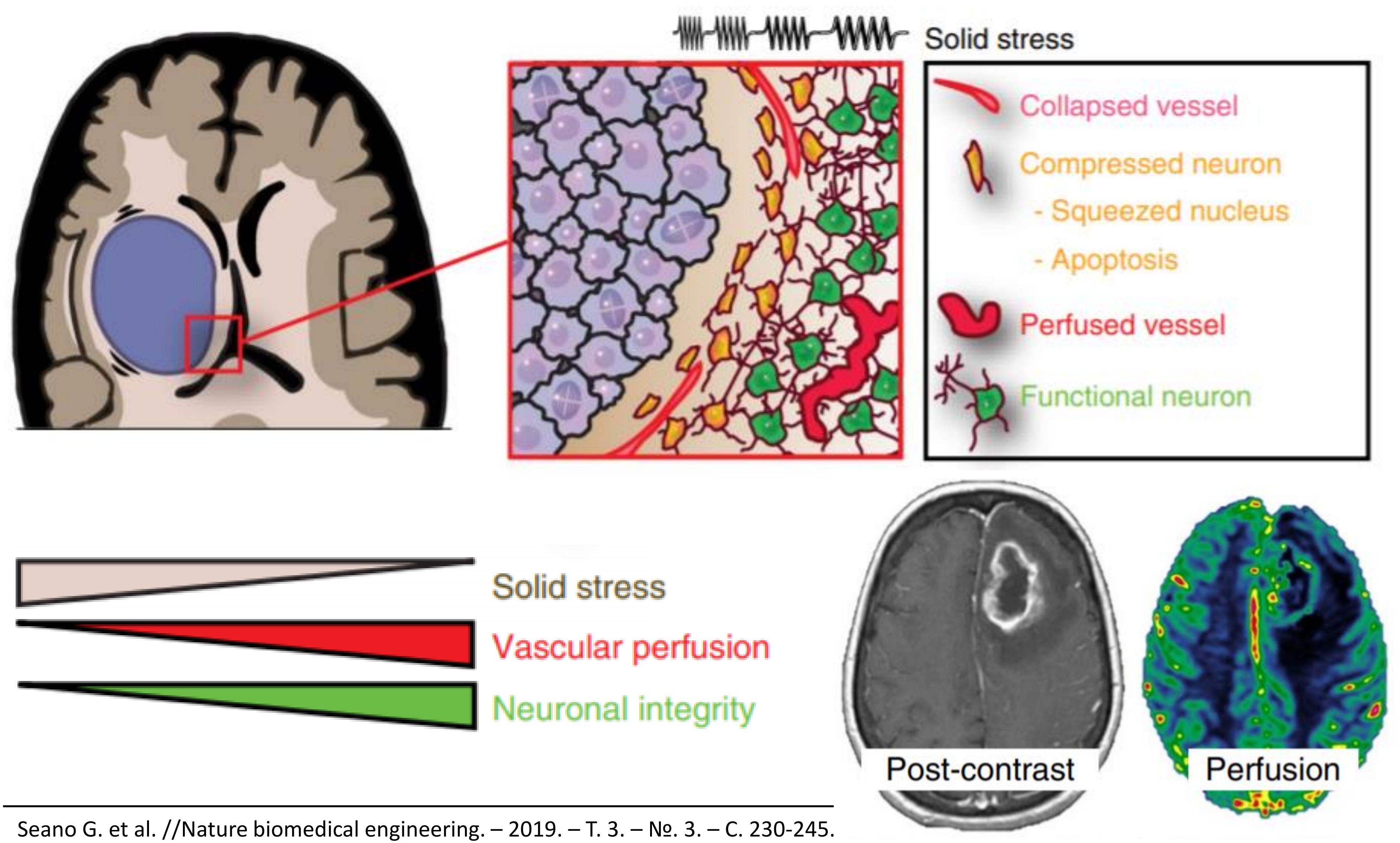


Gel release on 30th day



Helmlinger G. et al. //Nature biotechnology. – 1997. – T. 15. – №. 8. – С. 778-783.

Why model tumor growth with account of solid stress?



Seano G. et al. //Nature biomedical engineering. – 2019. – T. 3. – №. 3. – C. 230-245.

Main model assumptions

- Spherically-symmetrical growth
- Non-invasive tumor
- Avascular tumor
- Biphasic tissue (porous solid matrix immersed in fluid)
- Solid stress is isotropic
- Densities of two phases are equal and constant

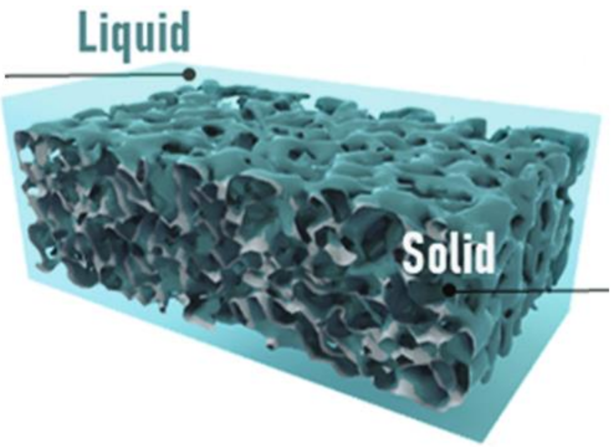
$$\text{solid phase:} \quad \frac{\partial c}{\partial t} = \overbrace{F(c,g,\sigma)}^{\substack{\text{production/}\\ \text{destruction}}} - \overbrace{\frac{1}{r^2}\frac{\partial(I_c c r^2)}{\partial r}}^{\text{convection}},$$

$$\text{interstitial fluid:} \quad \frac{\partial f}{\partial t} = \overbrace{-F(c,g,\sigma)}^{\substack{\text{production/}\\ \text{destruction}}} - \overbrace{\frac{1}{r^2}\frac{\partial(I_f f r^2)}{\partial r}}^{\text{convection}},$$

- Tissue is fully saturated: $c + f = 1$ => $I_c c = -I_f f$
- External body forces are negligible
- Fluid flow is slow
- Solid phase permeability is homogeneous (but varied)

Darcy's law: $f(I_f - I_c) = -\frac{K}{\mu}\frac{\partial p}{\partial r}$

Porous media theory: $\frac{\partial p}{\partial r} = -\frac{\partial \sigma}{\partial r}$



solid phase velocity

solid phase permeability

$$\boxed{I_c = -\frac{K}{\mu}\frac{\partial \sigma}{\partial r}}$$

fluid viscosity

solid stress gradient

Full model

tumor cells: $$\frac{\partial n}{\partial t} = \overbrace{Bn \cdot \Theta_p(g) \cdot \Theta_\sigma(\sigma)}^{\text{proliferation}} \overbrace{-Mn \cdot \Theta_d(g)}^{\text{death}} \overbrace{-\frac{1}{r^2}\frac{\partial(I_c n r^2)}{\partial r}}^{\text{convection}},$$

normal cells: $$\frac{\partial h}{\partial t} = \overbrace{-\frac{1}{r^2}\frac{\partial(I_c h r^2)}{\partial r}}^{\text{convection}},$$

glucose: $$\frac{\partial g}{\partial t} = \overbrace{Ph[1-g]}^{\text{inflow}} + \overbrace{\frac{D_g}{r^2}\frac{\partial^2(g r^2)}{\partial r^2}}^{\text{diffusion}} \overbrace{-Q_p n \cdot \Theta_p(g) \cdot \Theta_\sigma(\sigma)}^{\text{consumption by proliferating cells}}$$
$$\overbrace{-Q_q n \cdot \{[1-\Theta_p(g)] \cdot \Theta_\sigma(\sigma) + [1-\Theta_\sigma(\sigma)]\} \cdot [1-\Theta_d(g)]}^{\text{consumption by quiescent cells}},$$

$$\Theta_p(g) = [1+\tanh(\epsilon\{g-g_p\})]/2,$$
$$\Theta_d(g) = [1+\tanh(\epsilon\{g_d-g\})]/2,$$
$$\Theta_\sigma(\sigma) = [1+\tanh(\epsilon\{\sigma_{cr}-\sigma\})]/2,$$

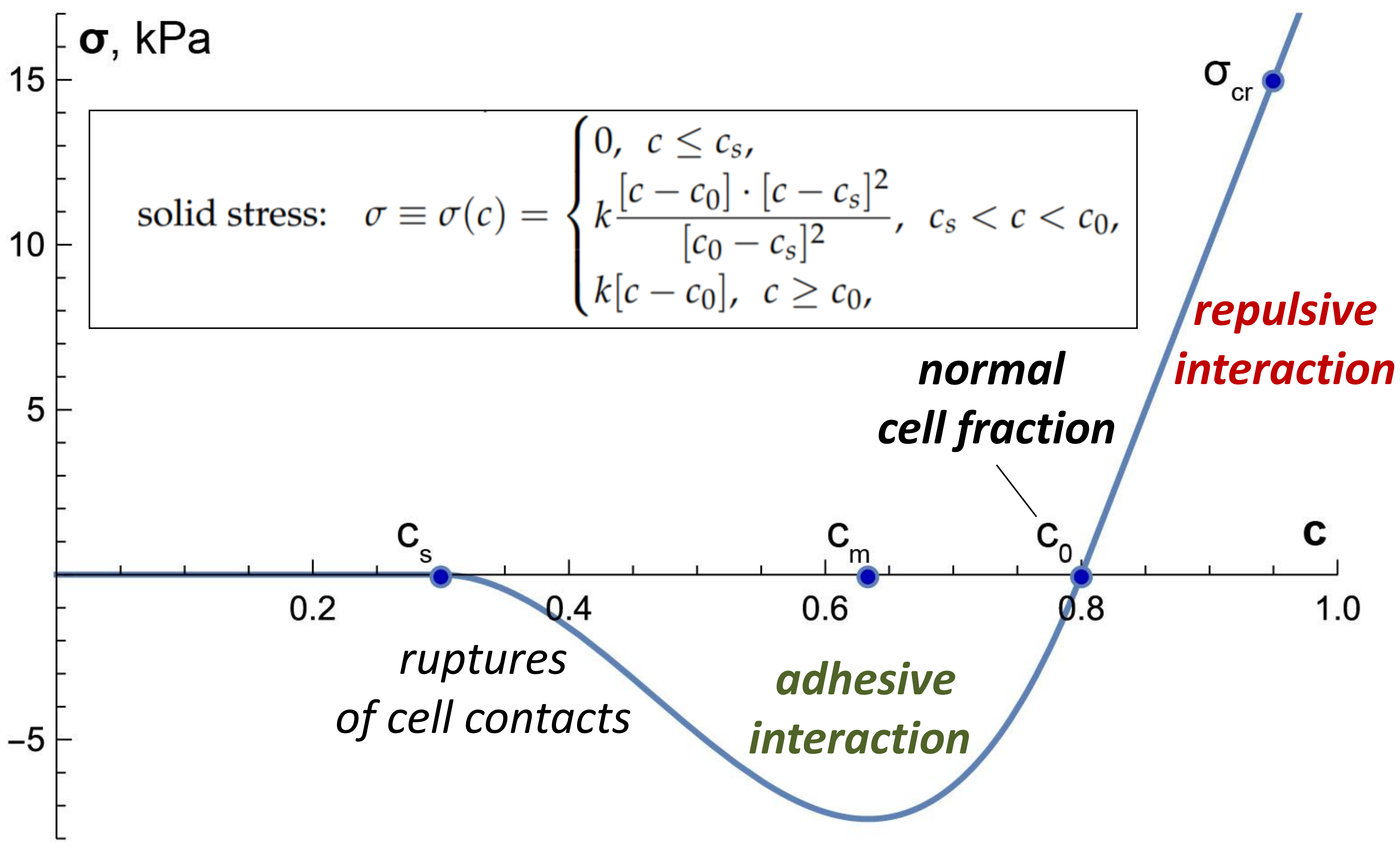
cells velocity: $$I_c = -\frac{K}{\mu}\frac{\partial\sigma}{\partial r},$$

solid stress: $$\sigma \equiv \sigma(c) = \begin{cases} 0, & c \le c_s, \\ k\dfrac{[c-c_0]\cdot[c-c_s]^2}{[c_0-c_s]^2}, & c_s < c < c_0, \\ k[c-c_0], & c \ge c_0, \end{cases}$$

$$c = n + h.$$

Variation of P:
0.7*10^{-6} – 1.8*10^{-4} s^{-1}
Variation of K/μ:
10^{-10}-10^{-6} cm^2/(mmHg·s)

Dependence of solid stress on cell fraction



Infinite hydraulic conductivity limit
(K/μ → ∞)

$$c = c_0$$
$$f = 1 - c_0$$

$$\cancel{I_c = -\frac{K}{\mu}\frac{\partial \sigma}{\partial r}}$$

$$\text{tumor cells:} \quad \frac{\partial n}{\partial t} = \overbrace{Bn \cdot \Theta_p(g)}^{\text{proliferation}} \overbrace{-Mn \cdot \Theta_d(g)}^{\text{death}} \overbrace{-\frac{1}{r^2}\frac{\partial(I_c n r^2)}{\partial r}}^{\text{convection}},$$

$$\text{normal cells:} \quad \frac{\partial h}{\partial t} = \overbrace{-\frac{1}{r^2}\frac{\partial(I_c h r^2)}{\partial r}}^{\text{convection}},$$

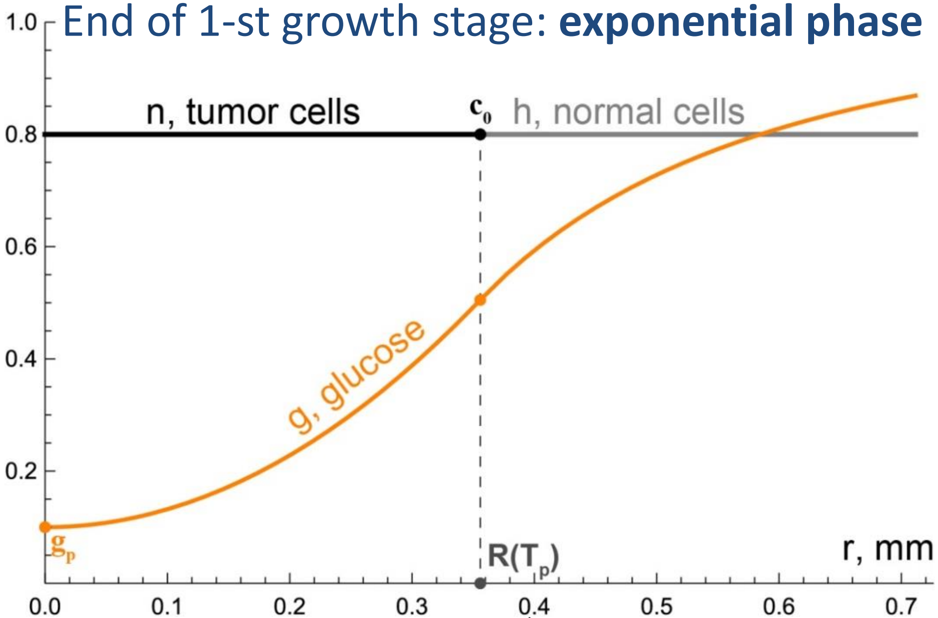
$$\text{glucose:} \quad \frac{\partial g}{\partial t} = \overbrace{Ph[1-g]}^{\text{inflow}} + \overbrace{\frac{D_g}{r^2}\frac{\partial^2(g r^2)}{\partial r^2}}^{\text{diffusion}} \overbrace{-Q_p n \cdot \Theta_p(g) - Q_q n \cdot [1-\Theta_p(g)] \cdot [1-\Theta_d(g)]}^{\text{consumption by proliferating and quiescent cells}},$$

$$\text{cells velocity:} \quad \frac{1}{r^2}\frac{\partial(I_c r^2)}{\partial r} = \frac{1}{c_0}[Bn \cdot \Theta_p(g) - Mn \cdot \Theta_d(g)],$$

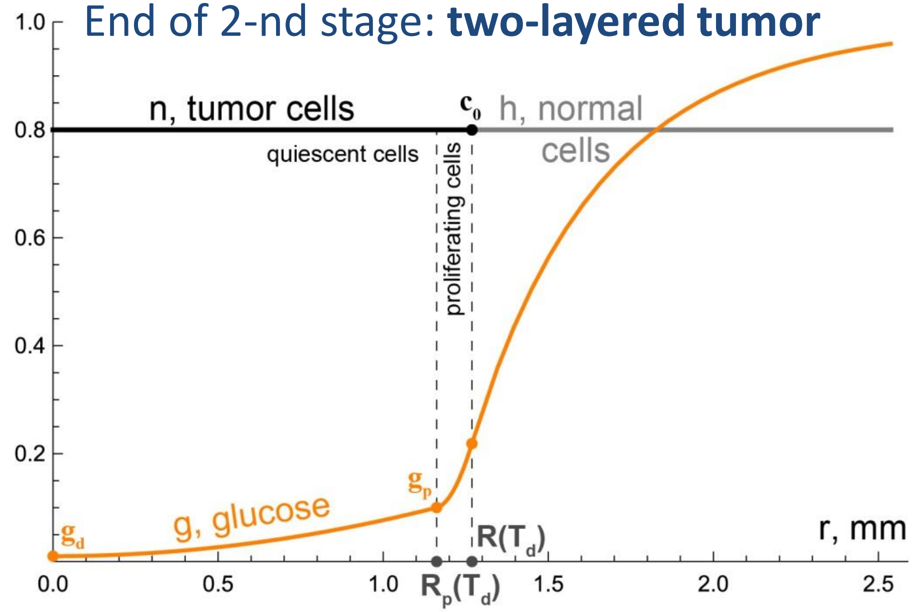
$$\boxed{\begin{aligned}\Theta_p(g) &= [1 + \tanh(\epsilon\{g - g_p\})]/2,\\ \Theta_d(g) &= [1 + \tanh(\epsilon\{g_d - g\})]/2.\end{aligned}}$$

Estimation of growth curves at $K/\mu \to \infty$

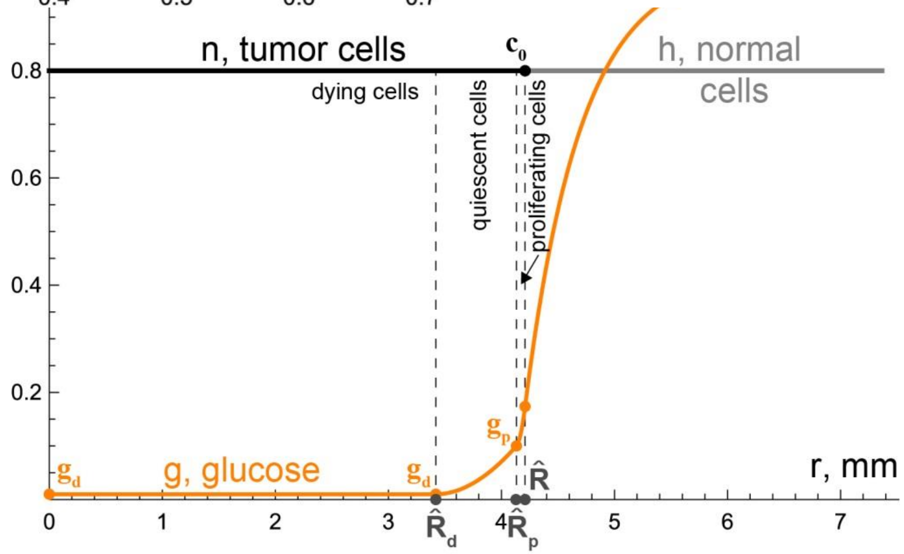
End of 1-st growth stage: **exponential phase**



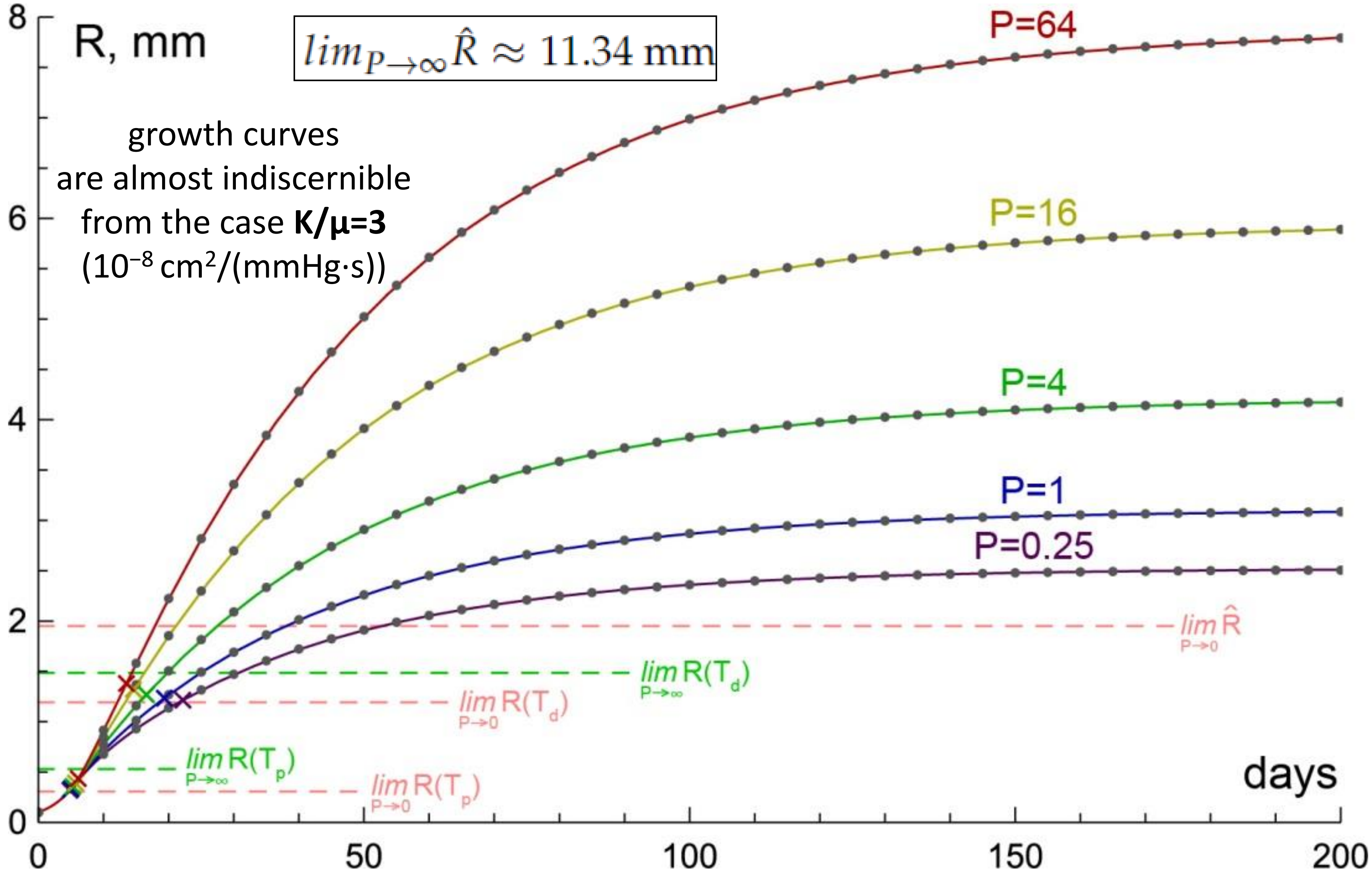
End of 2-nd stage: **two-layered tumor**



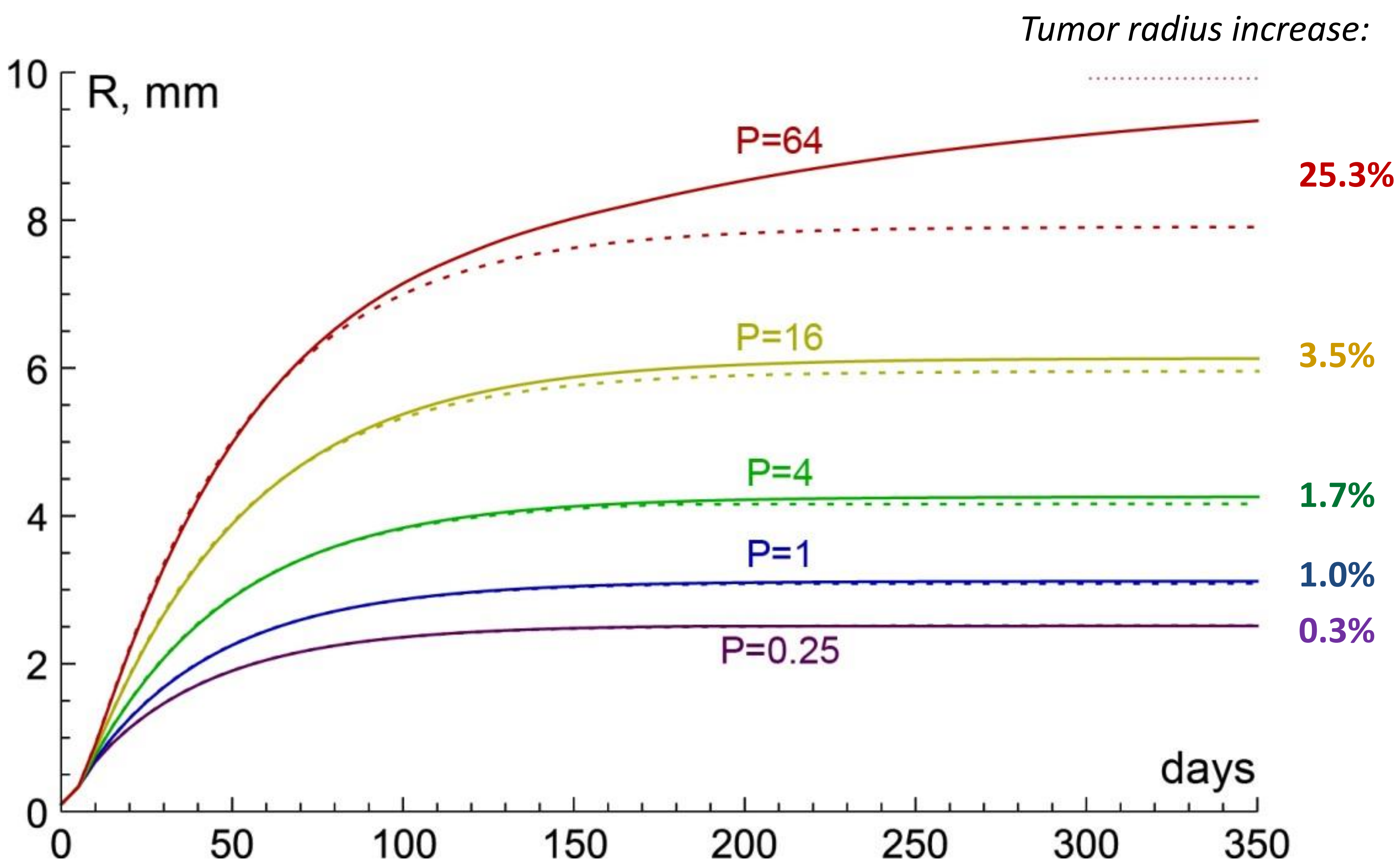
End of 3-rd stage:
stable state



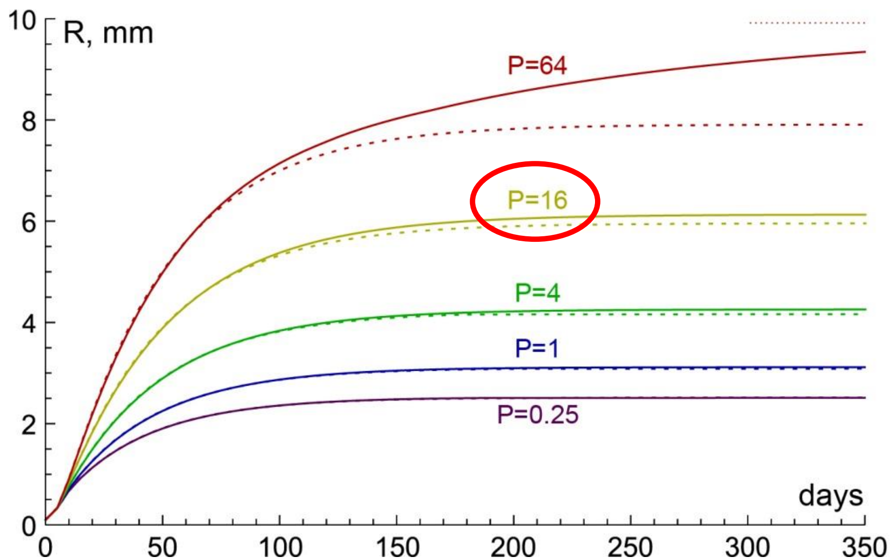
Growth curves and comparison with numerical simulations

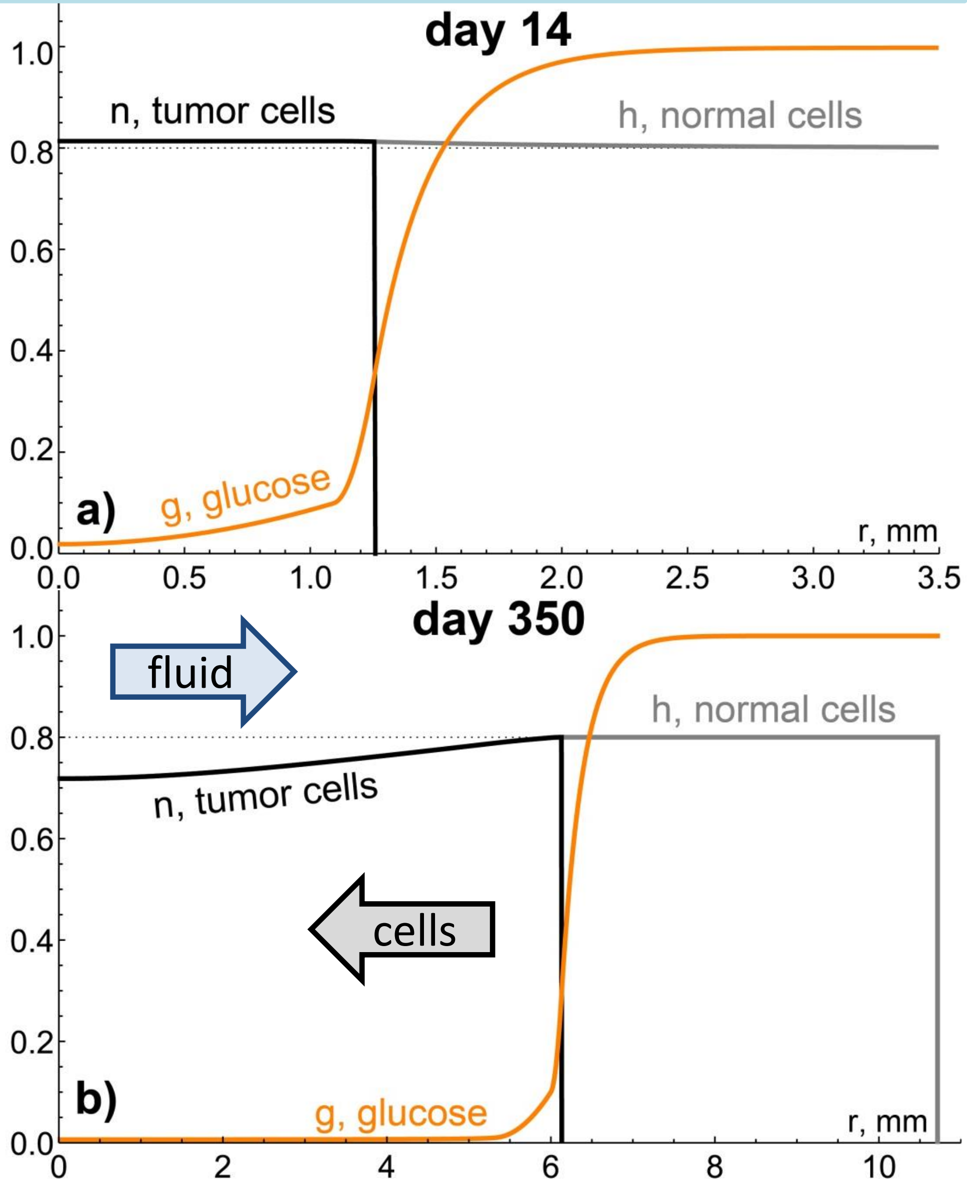


Intermediate hydraulic conductivity (K/μ=0.3)

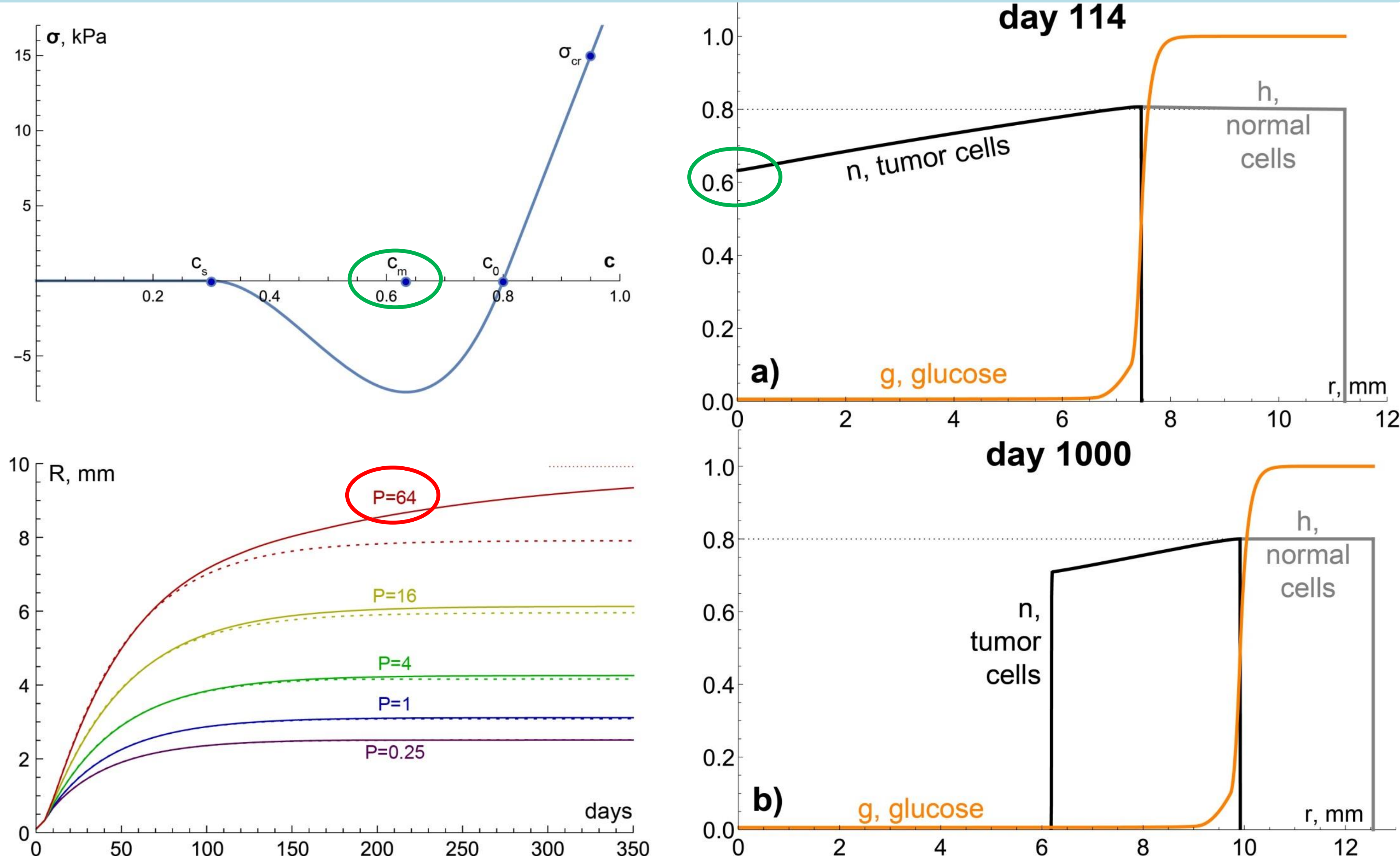


Intermediate hydraulic conductivity (K/μ=0.3)

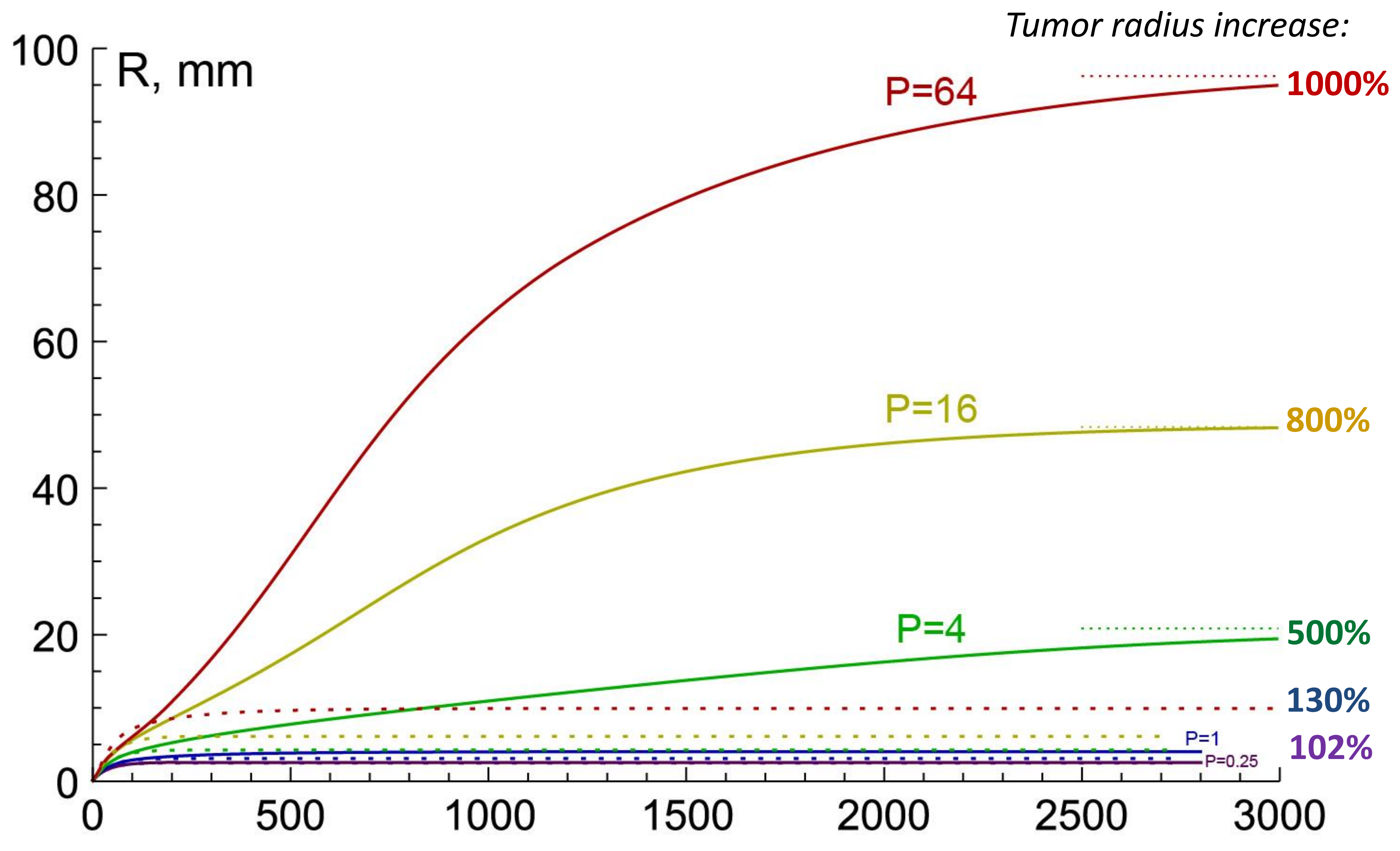




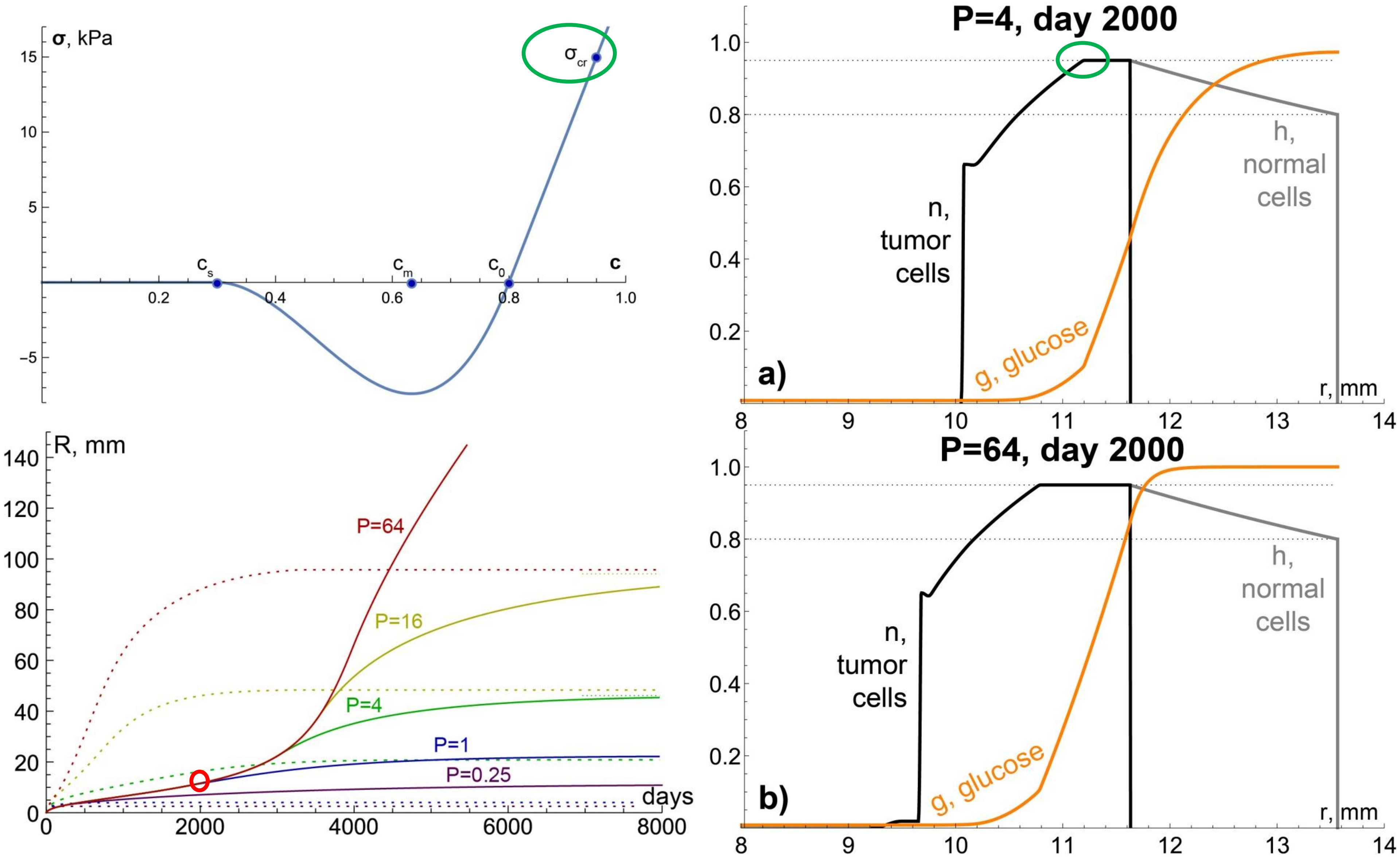
Intermediate hydraulic conductivity ($K/\mu=0.3$): fluid-filled core under high nutrient inflow



Low hydraulic conductivity (K/μ=0.03): crucial condition for giant benign tumors



Very low hydraulic conductivity (K/μ=0.003): stress-induced restriction and explosive acceleration



Discussion

Results:

- Simple continuous model of benign tumor growth in normal tissue was presented. **Nutrient supply and biomechanical interactions** were accounted for.

- In the limit of infinite tissue hydraulic conductivity
  accurate tumor growth curves were obtained semi-analytically.
  Such limit is applicable for $K/\mu > 10^{-8}$ $cm^2/(mmHg \cdot s)$.

- Sufficiently low hydraulic conductivity and high nutrient supply level
  led to **giant long-growing tumors**.
  Lowest values of tissue hydraulic conductivity and high nutrient supply level
  yielded **explosive tumor growth** before reaching plateau.

Most crucial model drawback: neglect of **circumferential stress.**

Future work: **optimization of tumor treatments**,
associated with the delivery of drugs via intravenous injections.

Thank you for your attention!

Results are published:

Kuznetsov M.
Combined Influence of Nutrient Supply Level and Tissue Mechanical Properties on Benign Tumor Growth as Revealed by Mathematical Modeling // Mathematics. – 2021. – T. 9. – №. 18. – C. 2213.

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