PATHOGEN-HOST RELATIONSHIP IN CAVITY DEVELOPMENT IN TUBERCULOSIS

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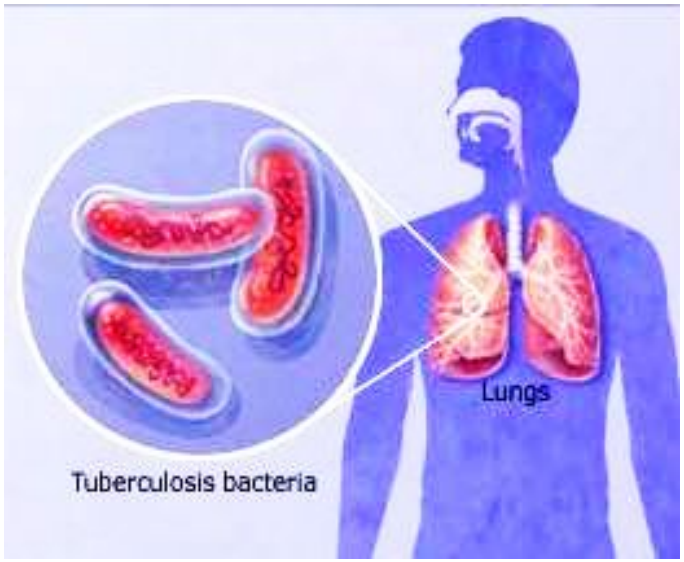
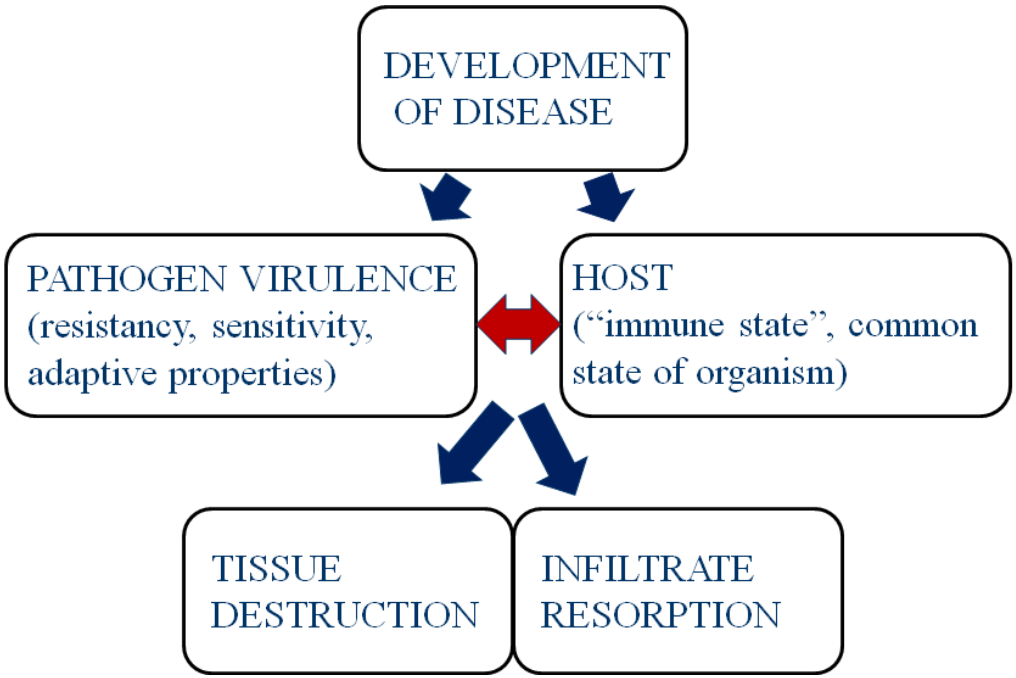
PATHOGENESIS OF TUBERCULOSIS



Forelled M. et al. *Virulence*, **4** (2013), 3

Elkington P. et al. *Eur Respir J*, **38** (2011), 456

Ong C. et al. *Pulmonary Perspective*, **190** (2014), 9



- *Micobacterium tuberculosis* "manipulates" by signalling pathways of immune response that results in the over-synthesis of matrix metalloproteinases
- Metalloproteinases play a central role in degradation of fibrillar collagens and other matrix components

TYPES OF TISSUE DESTRUCTION IN TUBERCULOSIS

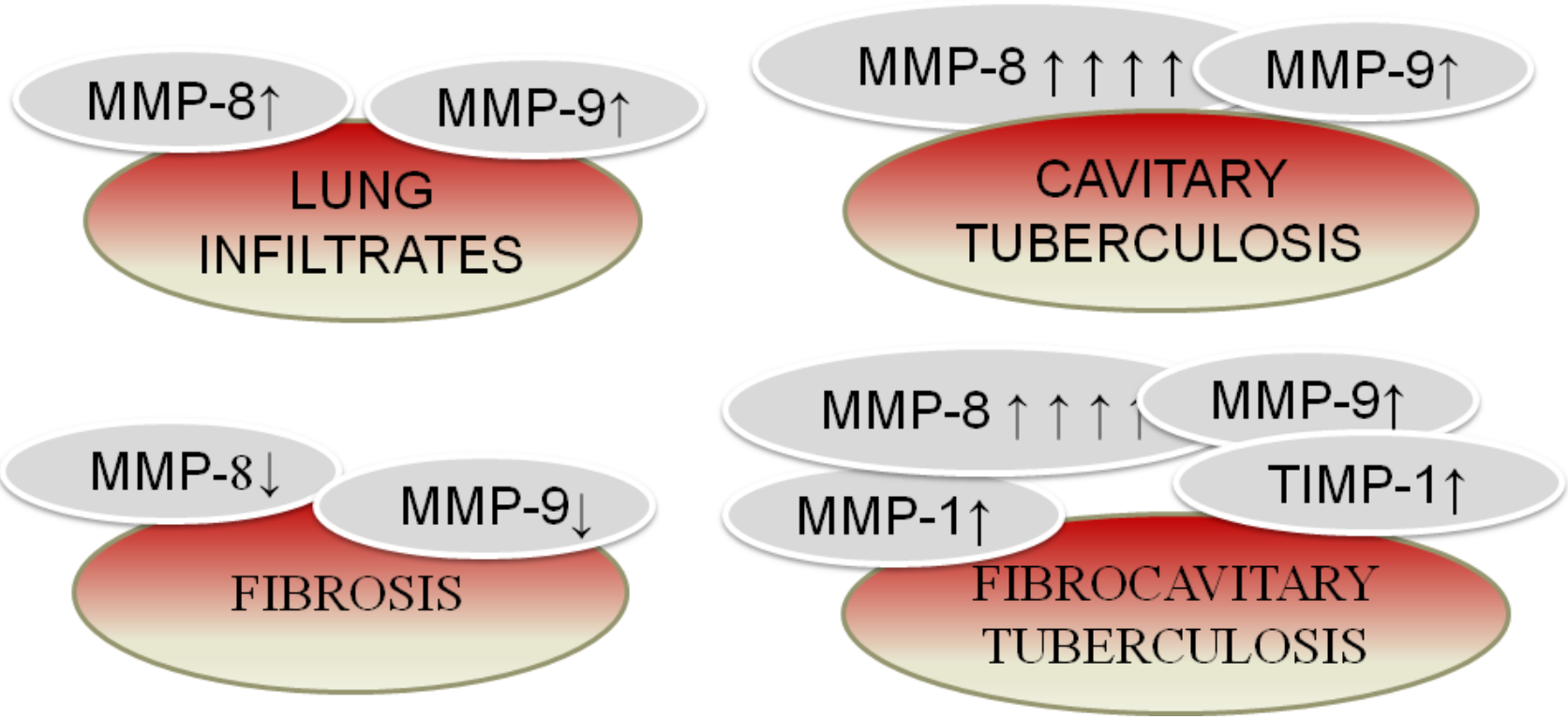
Examples of cavitary, fibrocavitary tuberculosis and fibrosis after treatment (Institute of Phtisiopulmonology, Saint Petersburg).

Local lung infiltrate in tuberculosis (Institute of Phtisiopulmonology, Saint Petersburg).

- MDR strains in most cases result in the cavity formation
- Successful treatment: cavity is replaced by fibrosis tissue
- Infiltrates are local regions in lungs and characterized by inflammatory changes, tissue necrosis and the presence or absence of destruction of lung tissue

BIOCHEMICAL MARKERS OF TISSUE DESTRUCTION: METALLOPROTEINASES

Clinical observations



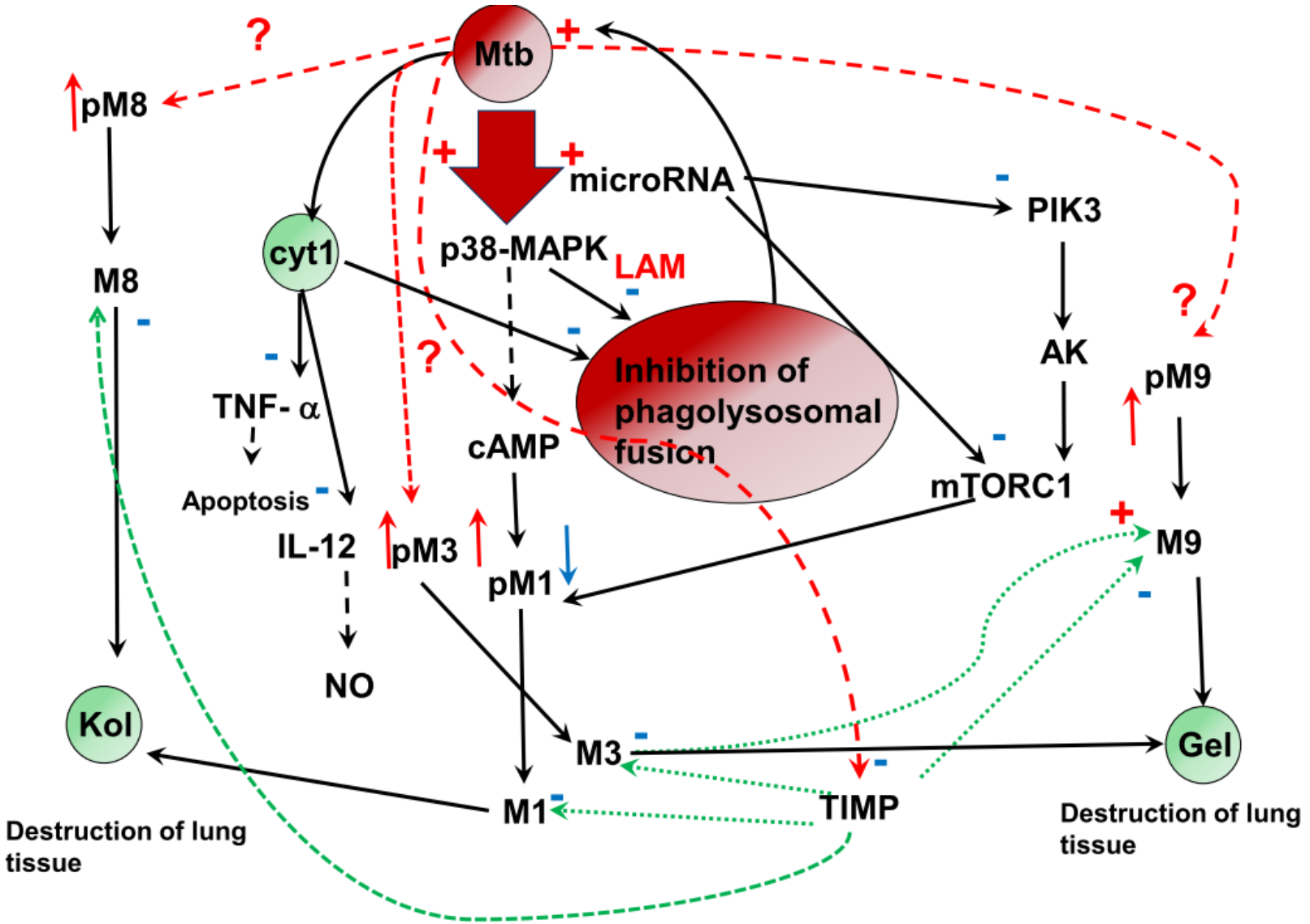
- MMP-1,MMP-3,MMP-8,MMP-9- different metalloproteinases
- TIMP- is inhibitor of MMPs

BIOCHEMICAL MARKERS OF TISSUE DESTRUCTION: METALLOPROTEINASES

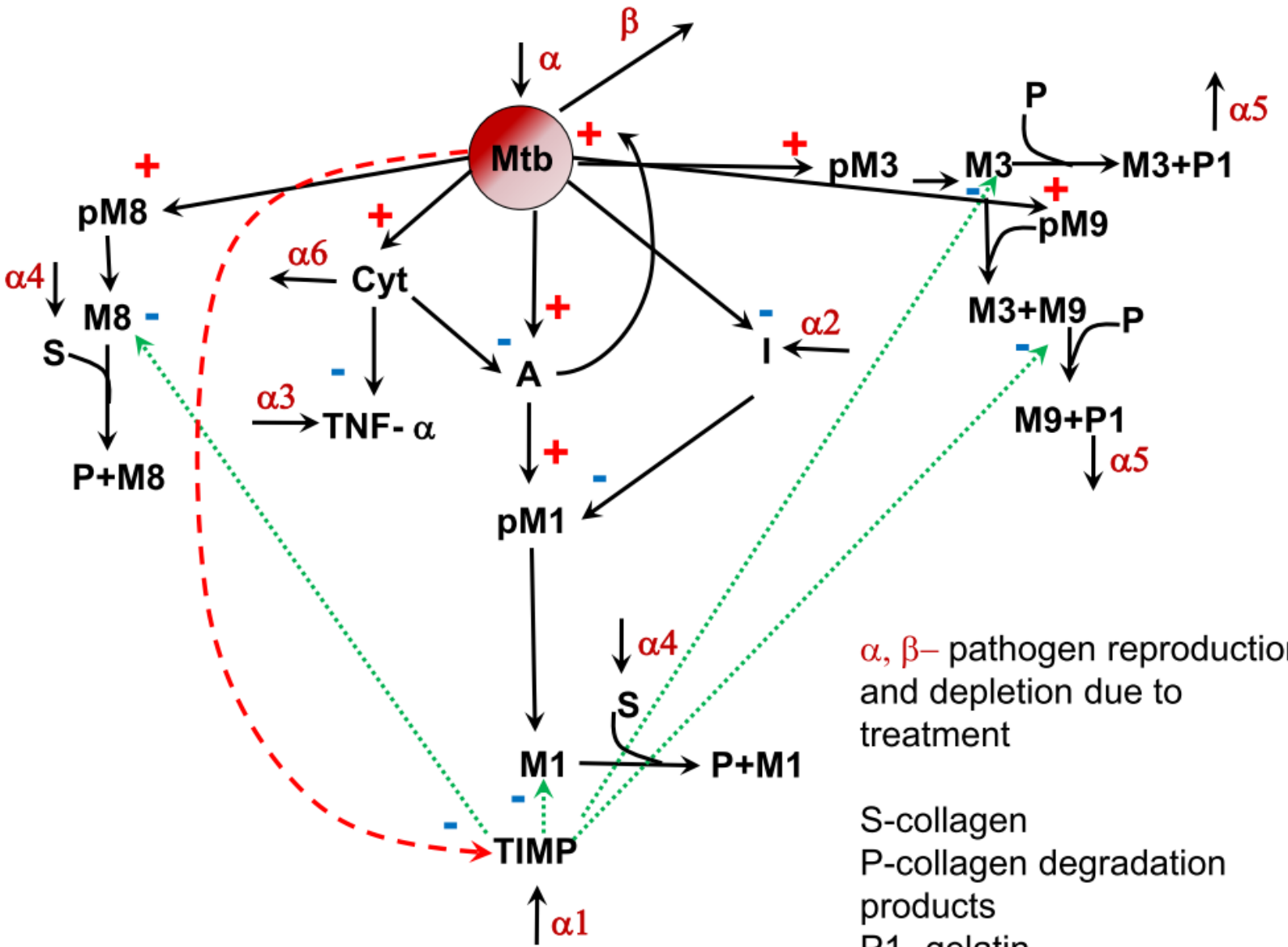
Challenges:

- What is an interplay between bacterial population dynamics and host cellular biophysical dynamics?
- How MMPs are connected with immune response and how their activity is regulated by the pathogen?
- Is it possible to use MMPs to prognose the treatment outcome?
- Clinical dates correspond to therapeutically target stages but not to dynamics

"MANIPULATION" BY REGULATORY PATHWAYS OF HOST TO INDUCE A TISSUE DESTRUCTION



SIMPLIFIED KINETIC SCHEME



SYSTEM OF EQUATIONS

$$\dot{Mtb} = \alpha + k_{react} A \cdot Mtb - \beta Mtb;$$

$$\dot{A} = k_A Mtb - k_{mt} b_1 A - k_{react} Mtb \cdot A - k_{AI} Cyt \cdot A;$$

$$\dot{I} = \alpha_2 - k_{MtbI} Mtb \cdot I;$$

$$\dot{TIMP} = \alpha_1 - k_{Mtbt} Mtb \cdot TIMP - k_{TIMP} TIMP \cdot (M1 + M3 + M8 + M9);$$

$$\dot{S} = \alpha_4 \exp(-Mtb) - k_{m1} S \cdot M1 - k_{m8} S \cdot M8;$$

$$\dot{P} = k_{m1} S \cdot M1 + k_{m8} S \cdot M8 - k_{m9} P \cdot M9 - k_{m3} P \cdot M3;$$

$$\dot{P1} = k_{m9} P \cdot M9 + k_{m3} P \cdot M3 - \alpha_5 P1$$

$$\dot{TNF} = \alpha_3 - k_{TNF} Cyt \cdot TNF;$$

$$\dot{Cyt} = k_{cyt} Mtb - \alpha_6 Cyt;$$

$$\dot{pM1} = k_{Mtb1} A - k_{pm1} pM1 - k_I I \cdot pM1;$$

$$\dot{M1} = k_{pm1} pM1 - k_{TIMP} TIMP \cdot M1;$$

$$\dot{pM3} = k_{Mtb3} Mtb - k_{pm3} pM3;$$

$$\dot{M3} = k_{pm3} pM3 - k_{TIMP} TIMP \cdot M3;$$

$$\dot{pM8} = k_{Mtb8} Mtb - k_{pm8} pM3;$$

$$\dot{M8} = k_{pm8} pM8 - k_{TIMP} TIMP \cdot M8;$$

$$\dot{pM9} = k_{Mtb9} Mtb - k_{pM8} pM9;$$

$$\dot{M9} = k_{pM8} pM9 - k_{TIMP} TIMP \cdot M9;$$

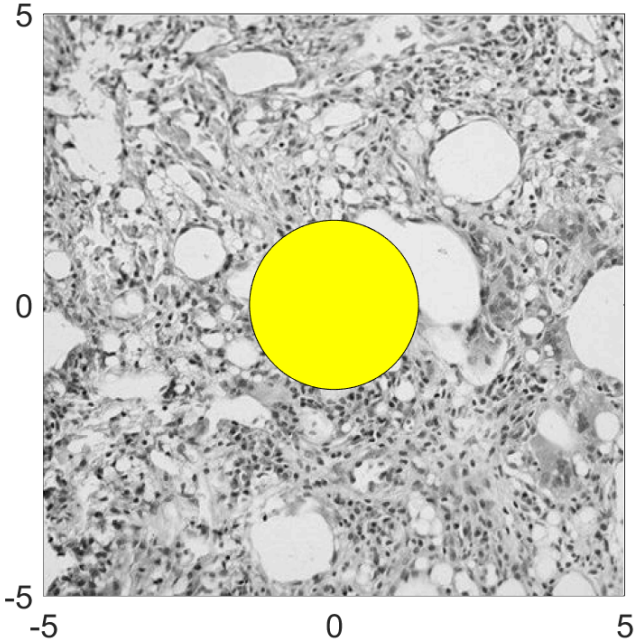
MODELLING OF RADII

Inflammation radius/outer fibrosis radius: $\mathbf{r_1} = r_0 \exp(-REG_1)$
Cavity radius/inner fibrosis radius: $\mathbf{r_2} = r_0 \exp(REG_2)$

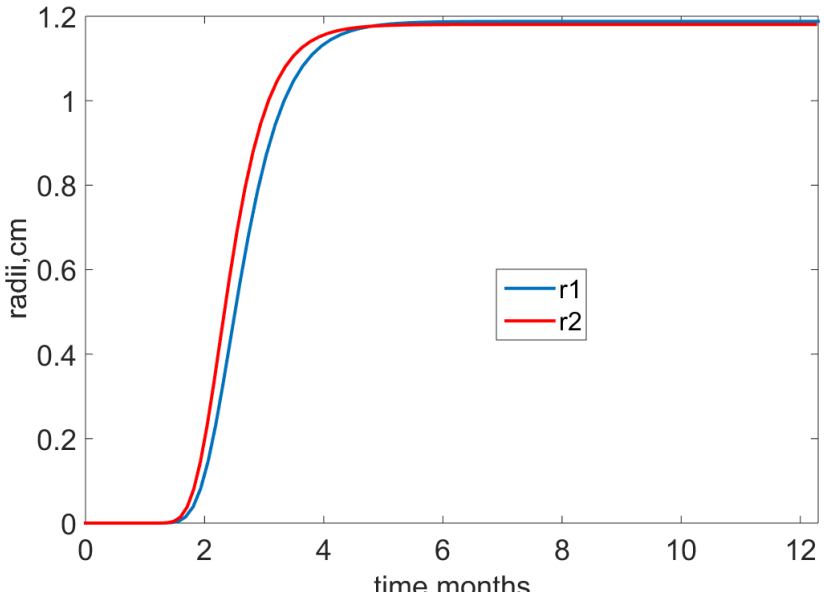
Metabolic regulators:

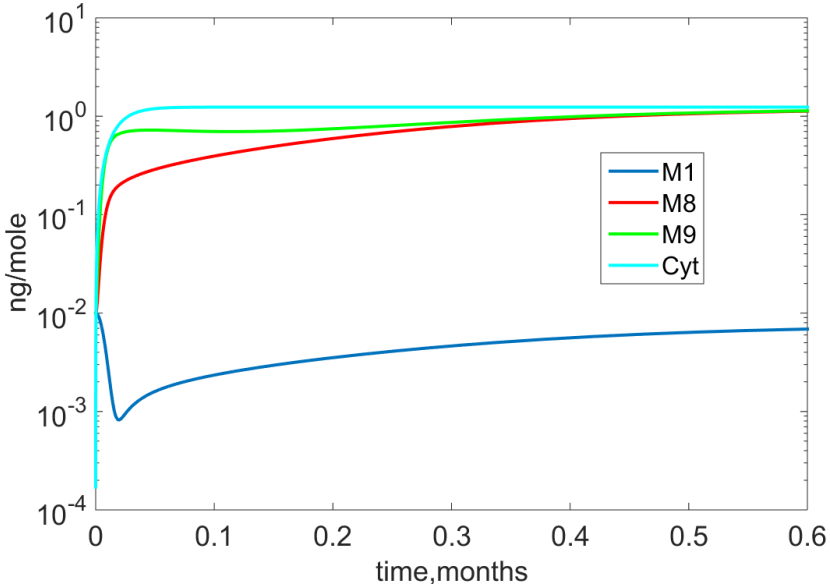
$$REG_1 = g_1 S - g_2(M1 + M3 + M9 + M8 + Cyt);$$
$$REG_2 = -g_3 S + g_4(M1 + M3 + M9 + M8 + Cyt)$$

CAVITARY TUBERCULOSIS

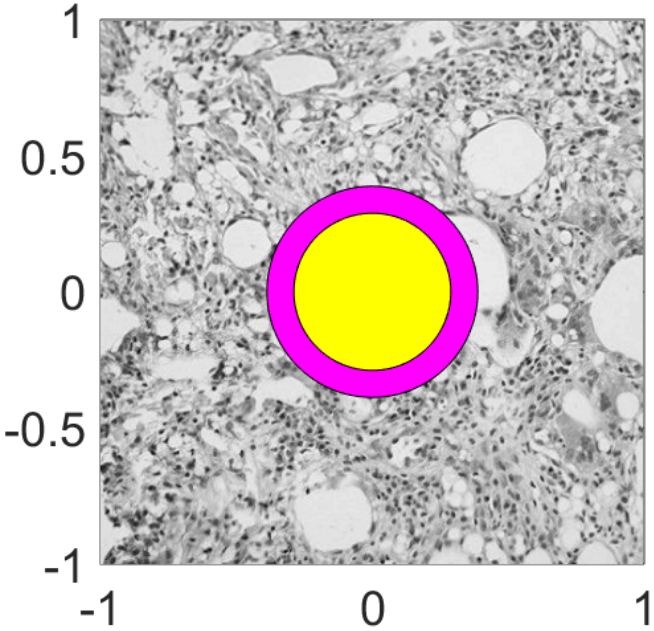


$$Mbt_0 = 5 \text{ cfu}$$
$$M1_0 = M8_0 = 0.01 \text{ ng/mole}$$
$$M3_0 = M9_0 = 0.01 \text{ ng/mole},$$
$$Cyt_0 = 0 \text{ ng/mole}$$
$$\beta = 0.17\ 1/\text{h}$$
$$g_2 = g_4 = 0.04$$
$$g_1 = 0.07, g_3 = 0.09$$

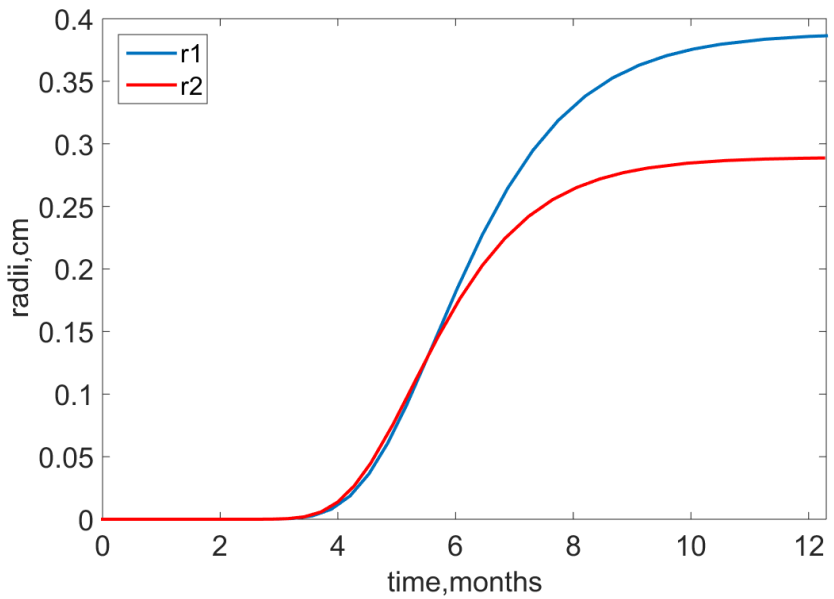


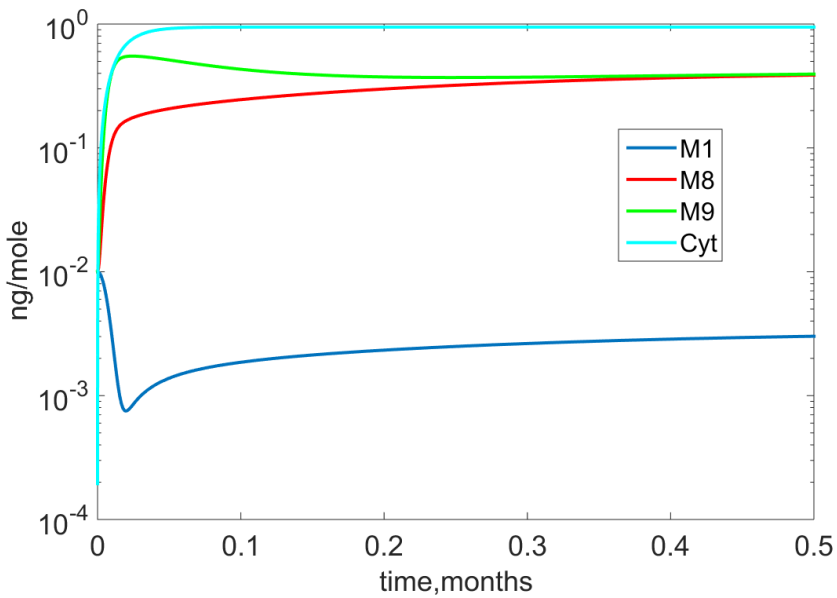


FIBROCAVITARY TUBERCULOSIS

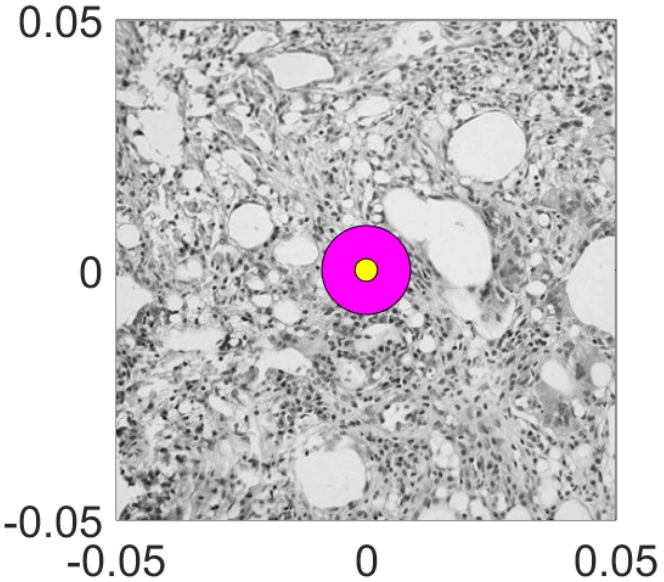


$$Mbt_0 = 5 \text{ cfu}$$
$$M1_0 = M8_0 = 0.01 \text{ ng/mole}$$
$$M3_0 = M9_0 = 0.01 \text{ ng/mole},$$
$$Cyt_0 = 0 \text{ ng/mole}$$
$$\beta = 0.22\ 1/\text{h}$$
$$g_2 = g_4 = 0.04$$
$$g_1 = 0.07, g_3 = 0.09$$

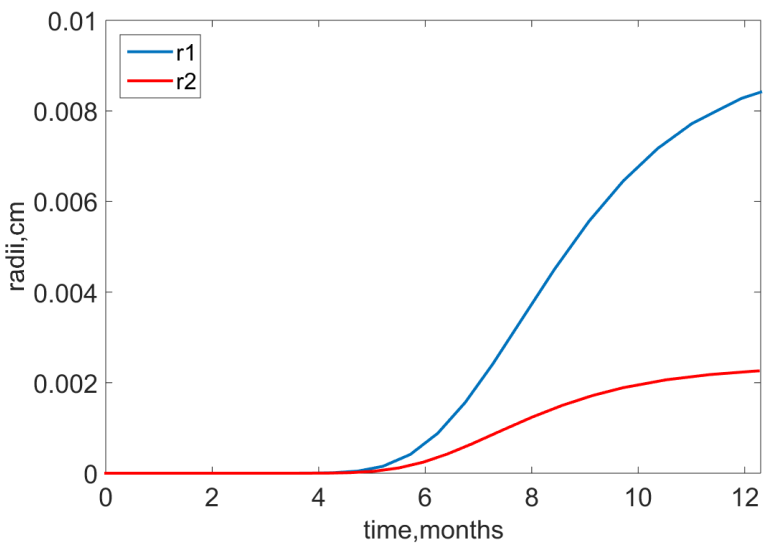


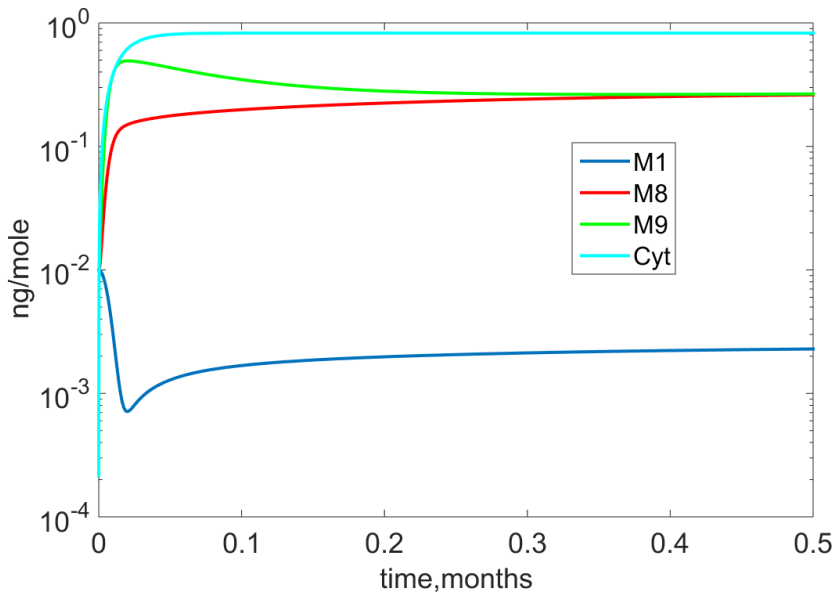


FIBROSIS

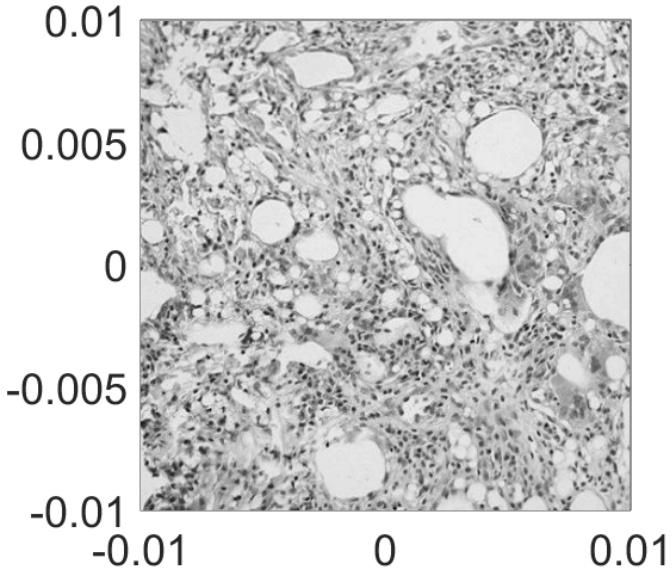


$$Mbt_0 = 5 \text{ cfu}$$
$$M1_0 = M8_0 = 0.01 \text{ ng/mole}$$
$$M3_0 = M9_0 = 0.01 \text{ ng/mole},$$
$$Cyt_0 = 0 \text{ ng/mole}$$
$$\beta = 0.25 \, 1/\text{h}$$
$$g_2 = g_4 = 0.04$$
$$g_1 = 0.07, g_3 = 0.09$$





COMPLETE INFILTRATE RESORPTION



$Mbt_0 = 5$ cfu

$M1_0 = M8_0 = 0.01$ ng/mole

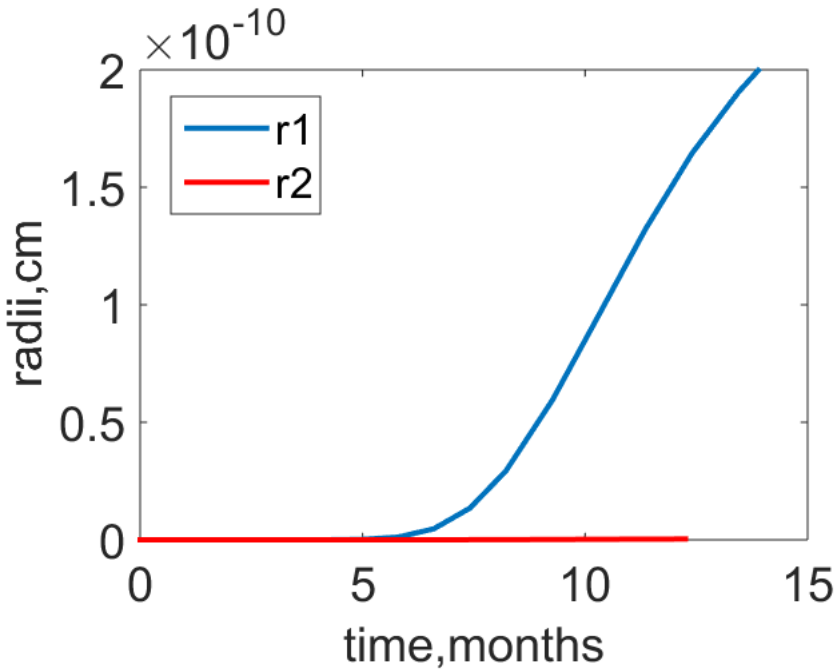
$M3_0 = M9_0 = 0.01$ ng/mole,

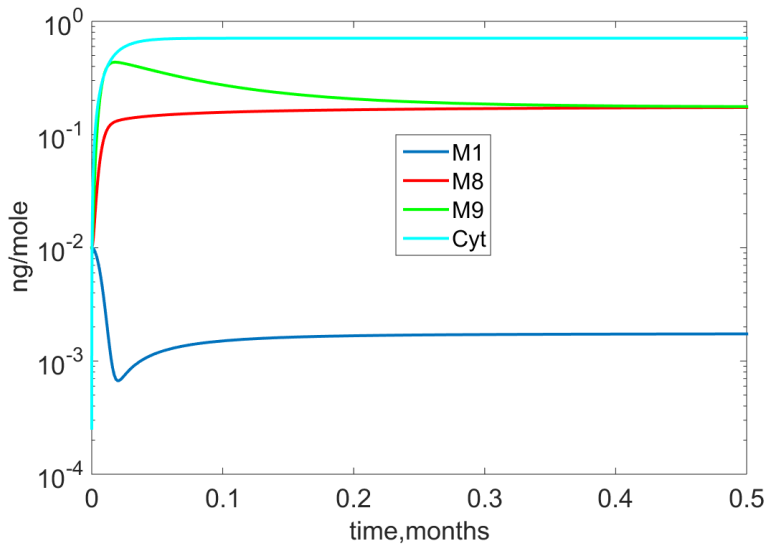
$Cyt_0 = 0$ ng/mole

$\beta = 0.32$ 1/h

$g_2 = g_4 = 0.04$

$g_1 = 0.07, g_3 = 0.09$





CONCLUSIONS

- The created model is concentrated on the description of key processes of host cellular pathway, which are manipulated by pathogen Micobacterium tuberculosis
- The key signalling pathways of the immune response are joined with a biochemical transformation of enzymes participating in tissue destruction
- The model reproduces qualitatively clinical data,namely three outcomes of the treatment: cavity,fibrocavitary process and infiltrate resorption
- The growth of inflammation hole and fibrosis capsule are modelled by two radii that depend on the dynamics of key metabolites of system