Dimensionality of motion and binding valency govern receptor-ligand kinetics as revealed by agent-based modelling

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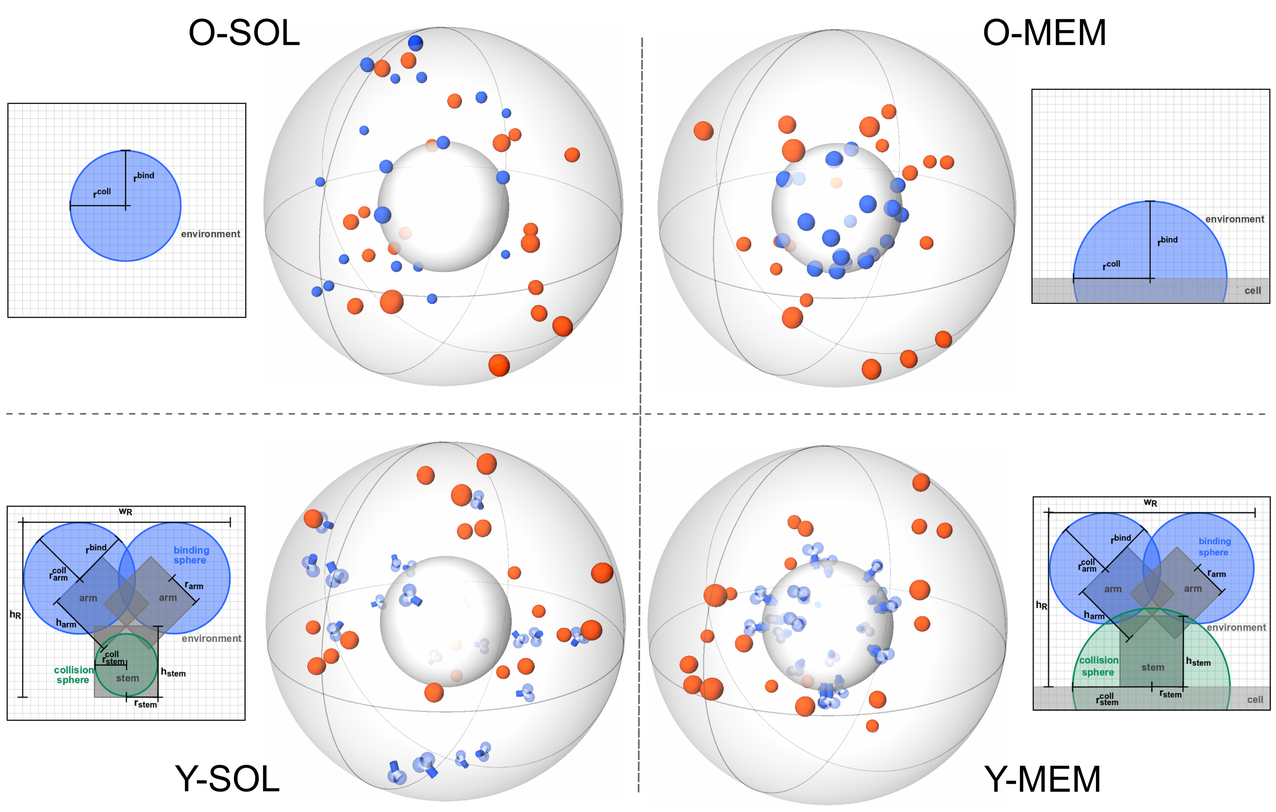
1. Aims of this study

This study focusses on the immune response by immunoglobulins which bind pathogen-derived antigens. In the human body, the peculiar Y-shaped immunoglobulins exist as soluble molecules and as membrane molecules on the B cell surface.

We aimed at establishing a quantitative mapping between macroscopic binding rates of an ordinary differential equation (ODE) model and their microscopic equivalents guiding the spatio-temporal Receptor Ligand (RL) binding by agent-based models (ABM). In this way, we revealed the impact of various receptor properties, such as their dimensionality of motion, morphology and binding valency, on the RL binding kinetics.

2. Microscopic modelling of RL binding by ABM



Central figures: The ABM variants are composed of the same spherical environment (large grey sphere) containing a spherical cell (small grey sphere) at the center. Ligands (orange) are always soluble, whereas receptors (blue) are studied in the variants: spherical receptor morphology in soluble (O-SOL) or membrane-anchored (O-MEM) form and Y-shaped receptor morphology in soluble (Y-SOL) or membrane-anchored (Y-MEM) form.

Outer figures: Two-dimensional projection of three-dimensional receptors of the ABM variants. Each receptor consists of binding spheres and collision spheres that may be overlapping in position and size. Ligands can bind by encountering a receptor's binding sphere but are prohibited to penetrate receptors by the collision spheres.

3. Macroscopic modelling of RL binding by ODE

$$R + L \underset{k_{off}^{macro}}{\overset{k_{on}^{macro}}{\rightleftarrows}} C$$

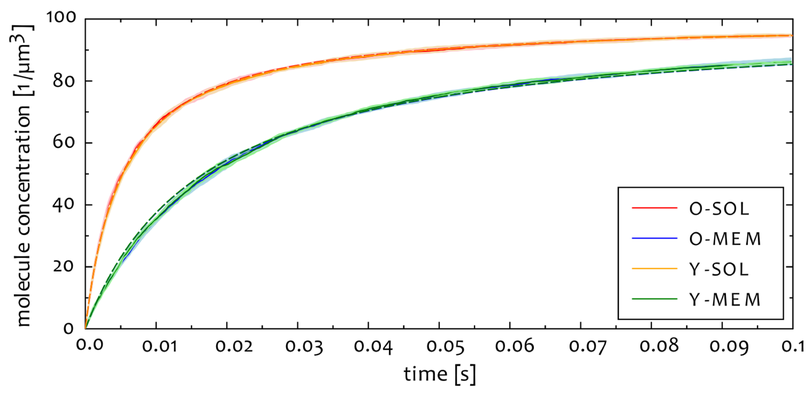
- Receptors (R) and ligands (L) bind with reaction rate k_{on}^{macro} and form a molecular complex (C)
- C dissociate with reaction rate k_{off}^{macro}

$$\frac{dR}{dt} = -k_{on}^{macro} RL + k_{off}^{macro} C$$
$$\frac{dL}{dt} = -k_{on}^{macro} RL + k_{off}^{macro} C$$
$$\frac{dC}{dt} = +k_{on}^{macro} RL - k_{off}^{macro} C$$

- ODE system represents time-dependent changes of molecule concentrations in a continuous and deterministic fashion
- ODE model can be analytically solved

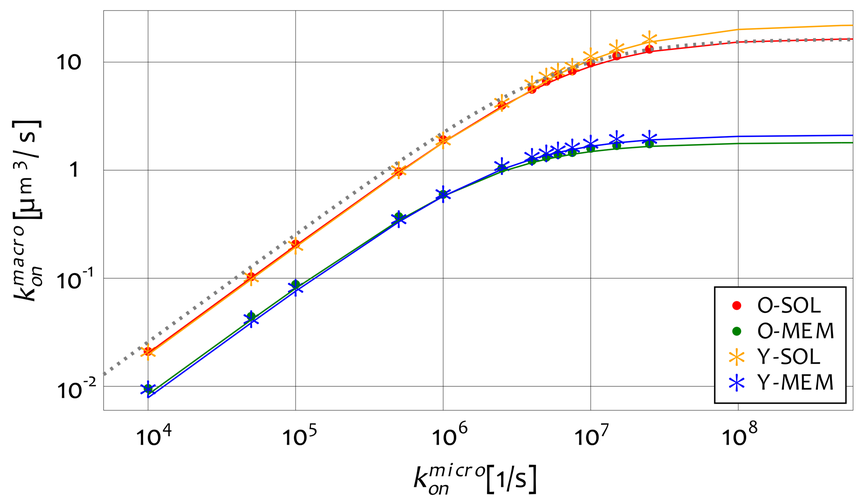
4. Binding kinetics for different receptor properties qualitatively comparable

- binding kinetics of the ODE model is in qualitative agreement with binding dynamics of all four ABM variants with monovalent receptors



Dark and pale lines in different colours represent, respectively mean values and standard deviations of 5 simulation runs per ABM variant with k_{off}^{micro} = 0.1 1/s and binding rate k_{on}^{micro}= 10^6 1/s. Dashed lines indicate the corresponding ODE models after fitting the macroscopic reaction k_{on}^{macro}.

5. Quantitative mapping of macroscopic and microscopic binding rates

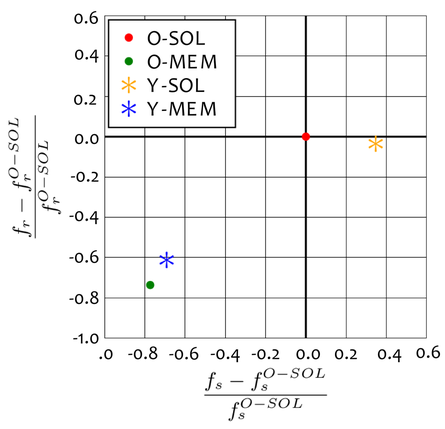


- numerical results resemble Hill functions: $$k_{on}^{macro}(k_{on}^{micro}) = \frac{a\, k_{on}^{micro}}{b + k_{on}^{micro}}$$
- agreement with theoretical considerations by Collins and Kimball [1]: $$k_{on}^{macro}(\kappa) = \frac{k_s\, \kappa}{k_s + \kappa}$$ $$\kappa = V_r\, k_{on}^{micro}$$
  > k_s denotes the diffusion-controlled reaction rate [2] $$k_s = 4\pi(r_L + r_R)(D_L + D_R)$$

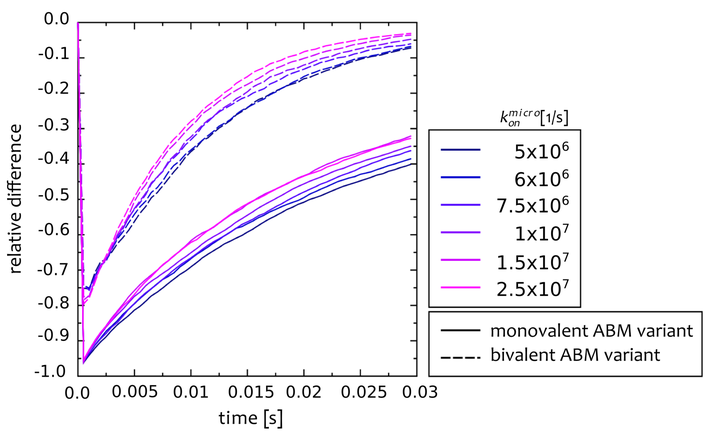
- scale mapping parameter

$$f_s = \frac{a}{k_s},$$
$$f_r = \frac{f_s\, k_s}{b\, V_r}$$

- compare quantitative difference in the scaling factors of ABM variants relative to O-SOL:



- quantitative difference between morphologies of monovalent receptors is vanishingly small
- major impact on RL binding of monovalent receptors caused by dimensionality of motion
- BUT: binding valency compensates differences in the binding kinetics of BCR and antibodies



Relative differences between ABM variants Y-MEM and Y-SOL with either monovalent or bivalent receptors

References:
[1] Collins, G., Kimball, F. (1949). Journal of Colloid and Interface Science
[2] Von Smoluchowski, M. (1917). Zeitschrift für physikalische Chemie

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